The Pop Test & Palisades Therapeutics Companies

Executive Summary

Diagnostics-Devices-Therapeutics

Randi Altschul, CEO
Neil Theise, MD, Lead Scientist

(201) 943-3770 Randi@PopTestLLC.com
www.PalisadesTherapeutics.com www.PopTestLLC.com

DIAGNOSTICS

Saliva diagnostic platform

Diabetes, NASH,

Cholesterol, Gout

1. What problem are we solving?

Saliva Diagnostic Platform for WELLNESS

Diabetes
NASH
Cardiovascular
Gout

Life Science Point of Care Testing

Real Time Health & Wellness Analytics

Upload data to cloud

Proprietary, Saliva Based Diagnostic Devices
Glucose-Diabetes
Cholesterol-Cardiovascular
Uric Acid-Gout
NASH/Fatty Liver Disease

Real Time answers for health and wellness with Digital Asset Management (DAM)
No Personally Identifiable Information

2. WELLNESS Screening/Monitoring

Diabetes

Diagnosed and undiagnosed diabetes in the United States, all ages, 2012,
Total: 29.1 million people or 9.3% of the population have diabetes.
Diagnosed: 21.0 million people. Undiagnosed: 8.1 million people.
(27.8% of people with diabetes are undiagnosed)

NASH/NAFLD

Prevalence of NAFLD and NASH is higher than estimated previously. Hispanics and patients with diabetes are at greatest risk for both NAFLD and NASH. Up to 80% of obese people have the disease. **Non-alcoholic steatohepatitis** (**NASH**) is the most extreme form of NAFLD, and is regarded as a major cause of cirrhosis of the liver of unknown cause. About 12 to 25% of people in the United States has NAFLD. While NASH affects between 2 to 5% of people in the United States.

Cholesterol

Percent of adults age 20 years and over with high serum total cholesterol (greater than or equal to 240 mg/dL): 13.4% (2009-2012)

Gout

Gout prevalence swells in U.S. over last two decades; Increase in obesity and hypertension are likely contributors
Prevalence of gout in the United States has risen over the last twenty years and now affects 8.3 million Americans.

3. The Pop Test saliva diabetes test was showcased at the American Diabetes Association 75thScientific Conference

Glucose PopTest: Saliva Glucose Measurements Reflect Blood Glucose Level in Diabetes Population

www.DiabetesPopTest.com

Neil D. Theise, MD; Rebecca L. O'Brien, BS; Myron C. Rapkin, MS; and Randice L. Altschul

PoP TEST

Introduction

Saliva glucose (SG) has long been considered a possible surrogate for blood glucose (BG) screening or monitoring in diabetes mellitus (DM), though limited sensitivities of reported assays have so far prevented this option (Table 1).

Table 1. Fifty-year literature survey regarding correlations of salivary vs. blood glucose in people with and without diabetes

First Author	Year	Journal	# non-diabetic patients	# diabetic patients
Positive correlations: Saliva and serum glucose				
Balan P	2015	J Clin Exp Dent	50	60
Gupta S	2015	J Diabetes Sci Technol	100	100
Sweeney MC	2010	DIACOMP	60	60
Jurysta C	2009	J Biol Rhythms	30	94
Yamaguchi M	2008	IEEE Eng Med Biol Mag	6	0
Arora S	2008	Ped J Nutrit Sci	25	135
Darwazeh AM	1991	J Oral Pathol Med	34	42
Mascetti P	1999	Diabetes Res Clin Pract	30	31
Reuterving CO	1987	Diabet Metab	0	12
Mascetti P	1996	Diabetologia	12	6
Correlations not significant or moderate/minimal, but saliva identifies hyperglycemia				
Aydin S	2010	J Biochem Mol Biol	23	40
Borg Andersson A	1990	Eur J Oral Sci	32	34
Kaufelaar EM	1996	Pediatr Dent	0	66
Ben-Aryeh H	1988	J Dental Complications	31	31
Correlations not significant: saliva and serum glucose				
Fushat et al	1991	J R Soc Med	0	31
Englander et al	1950	J Dental Research	26	26

We present a novel, rapid response, colorimetric, single-use, cost-effective Glucose PopTest (GPT) with sufficient readability, sensitivity, and specificity to accurately reflect BG levels in diabetic and non-diabetic individuals.

Devices were developed to:

- Sensitively detect glucose to saliva equivalents to 25 mg/dL of BG (i.e. approximately 0.25 mg/dL SG)
- Have a test pad that could evenly dispense saliva throughout the test pad independent of variations of saliva viscosity (intra- and inter-individual variations being common).

Methods

Two devices were evaluated:

GPT-1 ("unoptimized"; detecting down to 0.7 mg/dL SG) and a further optimized GPT-2 ("optimized"; detecting down to 0.25 mg/dL SG). Both can be read qualitatively/semi-quantitatively (visual color chart comparison) or quantitatively (digital reader). Figure 1 shows a sample of color range in response to changing glucose concentrations.

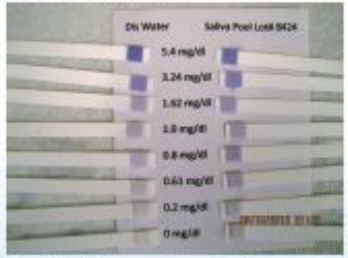


Figure 1. GPT-2 test strips response to glucose ranges in distilled water (left) and saliva (right).

Both devices require that the saliva sample be obtained >15 minutes after food ingestion and a water mouth rinse. GPT evaluations of screening for DM (n=123) and from glucose challenge study (n=154) indicated that SG is consistently ~1% of BG, independent of dental hygiene.

Results

GPT-1 (unoptimized) data (n=73):

- Accuracy/precision:
  - 100/96 vs. reference SG method (BioAssay System Enzychrom Glucose Test)
  - 44.4/92.9 vs. BG test using paired plasma samples (YSI Glucose Analyzer).
- Comparison of novice vs. expert color-chart reads showed ≥ 93% agreement (Figure 2).

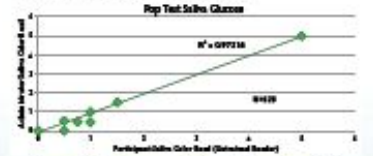
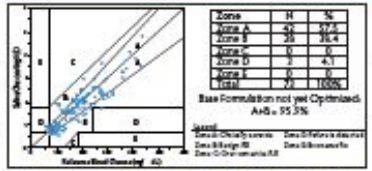


Figure 2. Novice vs. expert color-chart reads for GPT-1 (unoptimized) test for salivary glucose.

Comparison tests were administered 123 times for all points (0, 0.5, 0.75, 1.0, 1.5 and 5.0 mg/dL). The scatter for points (0.5, 0), (0.75, 0.5), and (1.0, 0.5) represent low readings on pre-training comparisons. Post-training, all points were identical between participants and experts indicating that training in color reading eliminated most to all descrepancies.

- Clarke error grid analysis (Figure 3) indicates 95.9% in zones A and B ("clinically accurate" and "benign Rx", respectively).



Zone	#	%
Zone A	52	57.1
Zone B	35	38.4
Zone C	0	0
Zone D	3	4.1
Zone E	0	0
Total	73	100%

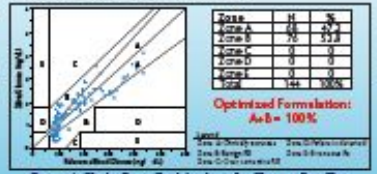
Base Formulation not yet Optimized.
A+B = 95.9%

Figure 3: Clarke Error Grid Analysis for Glucose Pop Test Device 1 ("unoptimized" base formulation) (n =73)

The diagonal represents the perfect agreement between the two, whereas the points below and above the line indicate, respectively, overestimation and underestimation of the actual values. Zone A (acceptable) represents the glucose values that deviate from the reference values by ≤20%, or are in the hypoglycemic range (≤70 mg/dL) when the reference is also within the hypoglycemic range. The values within this range are relatively near and are thus characterized by correct clinical treatment. Zone B (benign errors) is located down and below zone A; this zone represents those values that deviate from the reference values, which are overestimated by 20. The values that fall within zones A and B are clinically acceptable, whereas the values included in Zones C-E are potentially dangerous and there is a possibility of making clinically significant mistakes.

GPT-2 (optimized) data (n=144):

- Accuracy/precision
  - 100/100 vs. reference SG method
  - 90.0/93.2, vs. comparative plasma test using paired plasma samples.
- Regression analysis of GPT-2 results showed r = 1.0 vs SG ref standard and r = 0.822 vs BG.



Zone	#	%
Zone A	68	47.2
Zone B	76	52.8
Zone C	0	0
Zone D	0	0
Zone E	0	0
Total	144	100%

Optimized Formulation:
A+B = 100%

Figure 4: Clarke Error Grid Analysis for Glucose Pop Test Device 2 ("optimized" base formulation) (n =144)

Conclusions

- These data indicate that SG reflects BG in diabetic and non-diabetic individuals independent of oral hygiene.
- The Glucose PopTest sensitively and specifically measures SG confirming its viability for population screening for DM and possibly for pre-diabetes.
- These data also suggest that SG testing could reduce or eliminate needle-sticks for daily self-monitoring for people with insulin dependent DM.

References

- Amer S, et al. Saliva glucose concentrations in patients with diabetes mellitus – a statistically sensitive indicator for monitoring blood glucose levels. Pak J Pharm Sci 2005; 18: 15-7.
- Aydin S. A comparison of ghrelin, glucose, alpha-amylase and protein levels in saliva from diabetics. J Biochem Mol Biol Biophys Overview 2005; 8: 155-60.
- Balan P, et al. Can saliva offer an advantage in monitoring of diabetes mellitus? – A case control study. J Clin Exp Dent 2015; 7: e510-5.
- Ben-Aryeh H, et al. Saliva composition in diabetic patients. J Dental Complications 1988; 2: 96-9.
- Borg Andersson A, et al. Glucose concentrations in parotid saliva after glucose / food intake in healthy adults with glucose intolerance and diabetes mellitus. Eur J Oral Sci 1990; 98: 354-7.
- Darwazeh AMG, et al. Mixed saliva glucose levels and candidal carriage in patients with diabetes mellitus. J Oral Pathol Med 1991; 20: 280-3.
- Englander HR, et al. Concentrations in Blood Plasma and Parotid Saliva of Individuals with and without Diabetes Mellitus. J Dent Res 1950; 42: 1240.
- Fushat LH, et al. Glucose concentrations in parotid fluid and venous blood of patients attending accident clinic. J R Soc Med 1991; 74: 732-735.
- Gupta S, et al. Comparison of salivary and serum glucose levels in diabetic patients. J Diabetes Sci Technol. 2015; 9: 91-6.
- Jurysta C, et al. Salivary glucose concentration and excretion in normal and diabetic subjects. Journal of Biomedicine and Biotechnology 2009; article ID 430628.
- Karjalainen KM, et al. Saliva function in children and adolescents with insulin-dependent diabetes mellitus. Pediatr Dent 1999; 21: 306-11.
- Lopez ME, et al. Salivary determinations in diabetic children. Braz Dent J 2000; 11: 24-31.
- Mascetti P, et al. Decreased saliva glucose secretory rate: mechanism for detection of diabetic patients with normal neuropathy. Diabetes Res Clin Pract 1999; 7: 181-6.
- Mascetti P, et al. Saliva insulin concentrations in type 2 (non-insulin-dependent) diabetic patients and close non-diabetic subjects: relationship to changes in plasma insulin levels after oral glucose load. Diabetologia 1996; 39: 685-8.
- Reuterving CO, et al. Saliva flow rate and saliva glucose concentration in patients with diabetes and the influence of severity of diabetes. Diabetes Metab 1987; 13: 427-32.
- Sweeney MO, et al. Comparison of serum glucose and salivary glucose in diabetic patients. J Parenter Enteral Nutr 2010; 34: 613-5.
- Yamaguchi M, et al. Noninvasively measuring blood glucose using saliva. IEEE Eng Med Biol Mag 1999; 18: 59-63.

Pop Test LLC
36 Cecelia Ave
Cliffside Park, NJ 07010
(201)943-3770
Randi@PopTestLLC.com

4.

✔Painless
✔Efficient and easy
✔Reliable and Accurate
✔Inexpensive

Simple technologies like saliva based tests complimented
by precise electronic devices providing:

the benefit of more convenience,
reduced frequency of invasive testing,
real-time analytics
and
opportunities for vast distribution
of screening devices to GLOBAL COMMUNITIES
underserved by health professionals.

Creative Design of Embodiments Means:

No hindrances to scalability in India, China or elsewhere

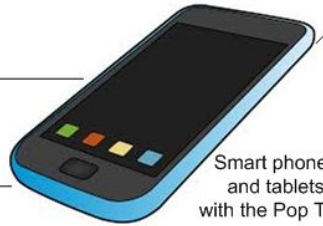
Readily adaptable to all environments and uses

- ✔ Low cost reagent
- ✔ Varied Embodiments can be made internationally and locally
- ✔ Leading to maximizing scalability and adaptability

5. The System

POP TEST
NON-INVASIVE & USER-FRIENDLY

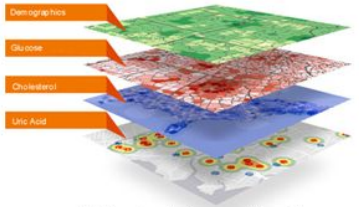
Pop Test strips for detection of glucose cholesterol uric acid in saliva



Smart phones and tablets with the Pop Test app can read the colorimetric results from the test strips and can receive real time data from physiology moniotor

Monitor your diet
Your Exercise
Your health trends
Prevent a metabolic even before it happens

All readings from the test strips are automatically uploaded to the Digital Asset Management platform provided by VideoBank



Meta Analysis provides the user with real time data on their health and well being including but not limited to
Diabetes
Cardiovascular
Gout
Wearable accessories for One Stop Health Tracking
Vital Signs
Heart
Pulse
Weight
Blood Pressure

Who needs this data?:

Primarily: The independent individual for management of their own health and well-being.

Secondary: Individual's Primary Care Physician

- Primary Care Physician's Medical Organization-Monitoring and Trending Individual
- Insurers-Health Care cost adjustments for healthy nutrition and exercise (lower co-pays).
- The Center for Disease Control (CDC) National Patterns/Trending Analysis
- Governments of Countries that provide single payer Health Care
- World Health Organization (WHO)-Global Monitoring and Analysis
- Health Care Industry-Development of better tools for self-management of health and well-being

- Real-time data on health, well-being and physical activity
- Self Monitoring of nutrition and physical activity-self awareness, self management
- Prevalence of elevated glucose events, binge eating events, exercise, weight fluctuation and Blood Pressure
- Occurrence of acute gout flare-up, hyper glycemia, frequency of events
- Prevention of hyper-glycemia episodes, gout flare-ups, and/or elevated cholesterol

6. VALIDATION:

Glucose Evaluation COMPLETED

Sensitivity/Specificity and Positive Predictive Value with identification of mitigating factors

Diabetes in Data Population

Blood glucose cutoff for lower limit, inclusive of Pre-Diabetes ≥126 mg/dl

Saliva glucose cutoff for lower limit, <44% Reflectance

(Saliva reflectance equivalent to 1.0mg/dl glucose in saliva

	Plasma Equivalent Positive	Plasma Equivalent Negative	
Pop Test Positive	74	4	PPV=94.9%
Pop Test Negative	1	96	NPV=98.9%
	Sens = 98.7%	Spec = 96.0%	

Early diagnosis is the key to success

- Production models completed
- Clinical Research phase completed
- U.S. & International Patents Awarded including formulas
- and manufacturing process
- Key medical, lab and FDA certified manufacturers contracted
- Smart Phone app reader in development

DEVICES

SMART PILLS

- ✔ Abuse Deterrent Technology
- ✔ Pill to Pill communication
- ✔ Microbiota sampling

Portable Artificial Liver

Abuse Deterrent Drug Delivery Device Using "Smart Pill"
Pill to Pill Communication

See 2 minute video: https://poptestllc.com/smartpillssavelives/

- **STOP OPIOID OVERDOSE**
- **STOP OPIOID THEFT**
- **STOP OPIOID DIVERSION**
- **STOP OPIOID COUNTERFEITING**

Problem:

Opioid Epidemic Cost to US Economy Surpasses a Trillion Dollars

Solution:

A “Smart Pill” complete end to end opioid prescription solution from manufacturer to user, that verifies adherence, deters over-dosage, prevents theft / diversion /and counterfeiting.

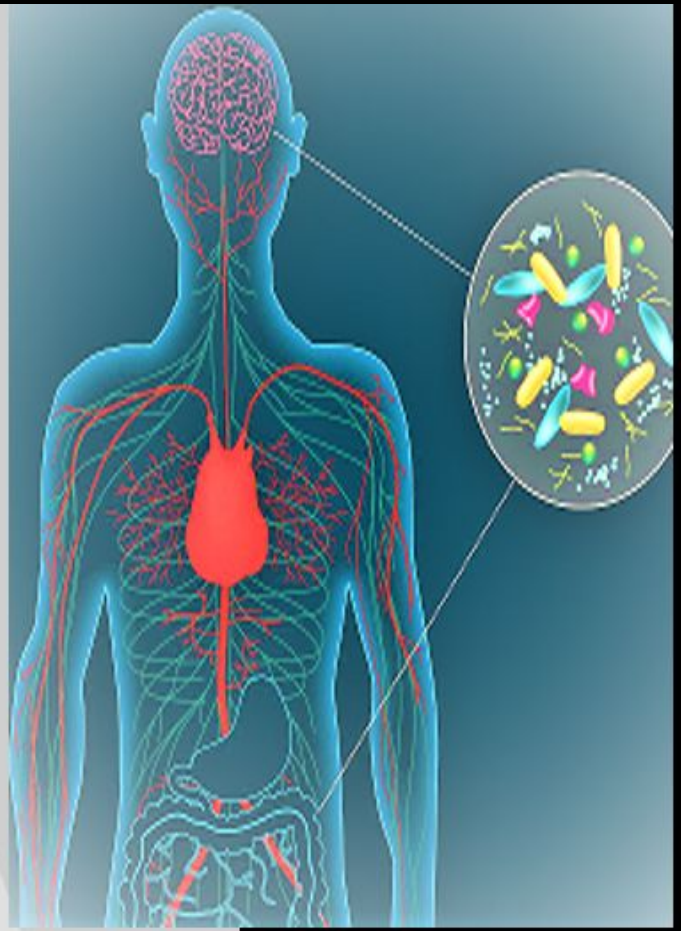
- *The SMART PILL* **has a built in micro encapsulated RFID chip that is preprogrammed by pharmacist**
- *The SMART PILL* **"knows" its correct practitioner prescribed dosage of the drug product**
- *The SMART PILL* **has a built in sensor to know if the drug product has been released into the system and controls additional release based on dosing instructions**
- *The SMART PILL* **"talks" to other SMART PILLS**
- *The SMART PILL* **only releases its drug product when it knows it is safe**
- *The SMART PILL* **carries a digital signature from the pharmacist who releases them to the patient**
- *The SMART PILL* **has a unique patient ID so if the wrong person gets it, the drug product will not release**

The Smart Pill was initially developed as an opioid delivery system for managing the opioid epidemic . Conceived as a device no bigger than a standard pill capsule, it has unique mechanical and wireless communication capabilities which can prevent dose escalation and overdoses and interfere with opioid theft and diversion. The same technology has now been modified to site specifically sample microbiota throughout the digestive tract. pH sensors and an internal clock allow the Smart Pill to target digestive tract locations. Four small doors open in the pill at the appropriate site, then close after microbiota sampling, after which the closed pill passes from the digestive tract and is then retrieved. These features will greatly accelerate research into the roles of microbiota in disease states of interest to ASPR and BARDA. Current planned studies, once the prototype has been completed, include: 1. An immediate human performance factor in military effectiveness is degradation of performance under stressful conditions, particularly sleep deprivation. Smart Pill, site specific sampling of digestive tract microbiota, comparing well rested vs. sleep deprived individuals, is considered a core component of this program of research being developed by collaborating physicians, scientists and engineers at the VA San Diego, UCSD Center for Pain Medicine, and the UCSD Jacobs Engineering School. 2. In traumatic brain injury and PTSD, microbiome alterations are strongly linked to cognitive, behavioral and physiological findings, but without greater precision, cannot be well understood. In both, settings, data discovered from Smart Pill site-specific microbiota research may then be turned around: the Smart Pill can become a drug or corrective microbiota delivery system rather than a sample collection device. Thus, knowledge gained from Smart Pill sampling will lead to Smart Pill delivery of novel treatments, in these instances to alter sleep deprivation-induced physiologic dysfunctions and to reduce the severity of neuropsychiatric dysfunctions and increased severity of infections in warfare-associated polytrauma including brain injury and PTSD.

Humans

Companion animals

Farm animals



GUT MICROBIOME-BRAIN AXIS

- **The gut microbiome is understood to be intimately involved with psychological and neurological states leading to distress, including conditions such as depression, bipolar illness, and post-traumatic stress disorder.**
- **Responses to traumatic brain injury, susceptibility to infections (including SARS-CoV-2/COVID-19), recovery from wounds, development of malignancy all have known associations with microbiome alterations.**
- **Smart Pills can sample microbiota for analysis of targeted regions of the digestive tract superior to state of the art analysis of microbiome composition**
- **Changes can be made with targeted drug or pro-biotic delivery for microbiome influenced neurologic and psychological conditions.**

What problem are we solving?

Liver Failure

A significant portion of health care spending is for recurrent treatments for chronic diseases. Given the liver's complexity, there are no simple or widely effective medical solutions to acute liver failure. The only long-term cure for acute liver failure is surgical transplantation. Regenerative medicine offers not only the potential to treat a variety of diseases, but more importantly, to potentially cure them.

What is our solution to the problem?

See 2 minute video:
https://vimeo.com/263967836/c60d29805b

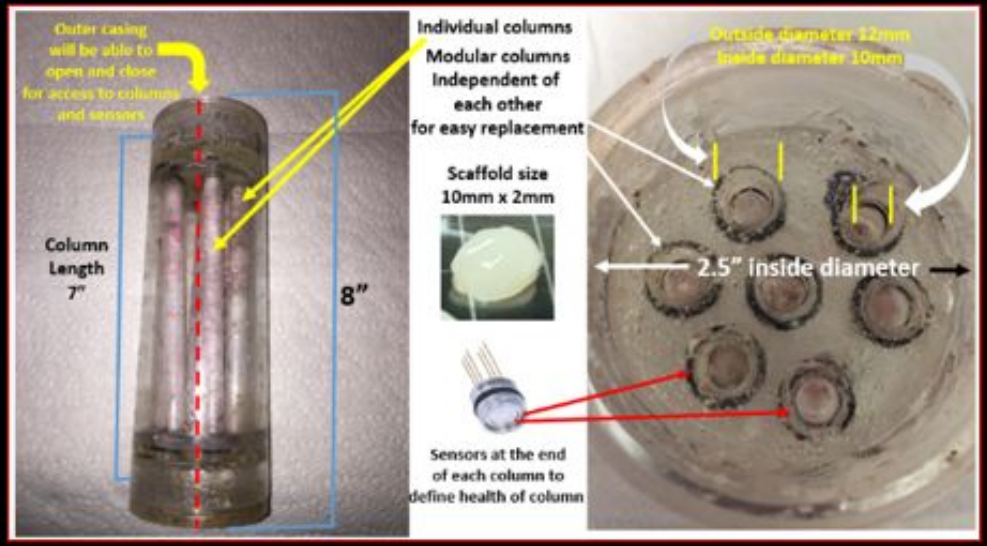
- A fully functional 3D liver culture system for active compound screening in liver drug discovery.
- A fully functional extracorporeal liver assist device for the treatment of patients in liver failure to bridge them to a whole organ transplant or allow their own liver to recover or in the treatment of chronic diseases.
- A transplantable, personalized bio-liver, alleviating the excessive wait time for patients on the liver transplant list.
- A transplantable, personalized bio-pancreatic islets with insulin production for treatment of type 1 diabetes.

Our **living human hepatic tissue columns** will be utilized to speed up the development of candidate compounds. Aspects of drug metabolism and/or effects of medications on hepatocyte diseases/injuries can be explored in functioning human tissue with a full range of tools, including histological, immunohistological and molecular markers.

A unique liver scaffold culture system for early stage drug testing to use before investing time & money in *in vivo* models

"Columns to produce Cures"

A Portable-Modular Artificial Liver/Pancreas
To extend and Save LIVES



Unlike artificial matrices such as those generated by 3D tissue printing, our native structure, decellularized liver scaffolds still hold key signaling components (i.e. GAG-proteins, HGF, IGF-BP3) which are necessary to fully mimic the natural hepatic microenvironment. Our system will allow pharma to go beyond bio-printing technology, giving them more and better avenues to filter and reject an ineffective or dangerous drug in a matter of weeks to months. This will shorten the drug discovery process and results in significant savings.

THERAPEUTICS

Oncology

PT150 and PT157: novel selective **Glucocorticoid & Androgen Receptor Antagonist/Modulators for Oncology** that represent a new class of small molecule anti-cancer drugs that pass through the Blood Brain Barrier

PT150:

- TRL-7 with multiple IND's is a re-purposed clinical stage small molecule with a large safety database in multiple clinical trials, including fifteen phase 1 studies and five phase 2 studies (depression).
- Immediatedly ready for human expanded access trials.

PT157: a preclinical compound (TRL 3-4) and requires IND enabling studies.

Multiple patents granted and pending

PT162 was designed to act as a protein p53-reactivating cell cycle checkpoint inhibitor, inducing cancer cell cycle arrest and/or apoptosis by restoring DNA-binding activity of mutant p53 protein.

- PT162 is part of an extended patent platform of PT Series 16 molecules.

Palisades Therapeutics High Value Advanced Partnering Opportunity

- **Extensive Intellectual Property Estate**

PT150

- **Composition of Matter**
- **Method of Use**
- **Date Exclusivity**

PT157

- **New Molecule**
- **Composition of Matter**
- **Method of Use**
- **Date Exclusivity**

PT162

- **New Molecule**
- **Composition of Matter**
- **Method of Use**
- **Date Exclusivity**

- PT150: Re-purposed NCE from Big Pharma CNS Program
  - Phase 2 compound
  - Extensive preclinical & clinical database
  - Clean safety database in humans & animal models.
  - New IND established for prostate cancer
- PT157: NCE derivative of PT150
  - Early pre-clinical data suggests greater potency than PT150
  - IND enabling studies required
- PT162 : p53 reactivator
  - Early pre-clinical data suggests that PT162 induces apoptosis by activating p53, several known candidates of p53 are activated, some even to 10-20 fold which is a huge signal in drug interaction studies.
  - IND enabling studies required

Glucocorticoid & Androgen Receptor Antagonist/Modulators for Oncology

GR-antagonists/AR modulators offer a new mechanism in the treatment of cancer by modulating crosstalk of the GR/AR pathways that are key factors in cancer cell proliferation. Palisades has a proprietary platform of small molecules in this class, with demonstrated activity as monotherapy or in combination therapy with other therapeutics in difficult to treat tumor cell lines and ex-plants. Lead compound, PT150, offers the further advantage of being a re-purposed clinical stage therapeutic.

- **FDA assigned IND#144686**
- **Recent studies in resistant prostate cancer model show PT150 efficacy better than enzalutamide**
- **Ph2 Proof of Concept study in patients can start 2023:**
  - **First-in-patient study of PT150 in patients with high-risk prostate cancer in adjuvant and salvage setting**
  - **Lead in Safety cohort with n=3 to 6 pts**
  - **Expansion cohort with n=15 subjects**
  - **Primary clinical endpoint: PSA / time to biochemical recurrence (BCR)**
  - **Secondary endpoints: Immune monitoring, etc**
- **Pivotal study could start early 2024, with potential NDA submission in 2025**

Castrate Resistant Prostate Cancer

Data suggest drug resistant metastatic prostate cancer population could be attractive initial entry into oncology for GR antagonist compounds

Significant lifecycle opportunities

- New anticancer mechanism demonstrated in refractory metastatic cancer settings both as a single agent and as a chemo-sensitizer.
- Extensive NIH NCI screening program and particular activity shown in xenograft models of breast, and ovarian cancer. (Daniel Von Hoff, MD Td2/TGEN)
- New data in prostate cancer explant studies show marked down-regulation of androgen receptors, in addition to glucocorticoid receptor blockade. (Mt. Sinai)
- New “explant” data (PT150 & PT157) in prostate. Pancreatic, and glioblastoma data very encouraging

Castrate Resistant Prostate Cancer: Tumor Clone Assays

Clones developed from human tumor over 8 month period which:

✓ are highly aggressive

✓ are highly treatment resistant

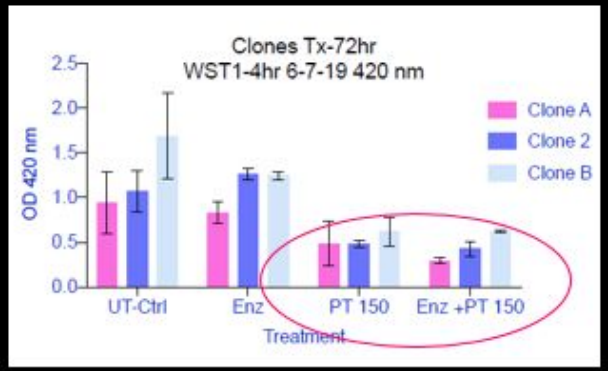
✓ have poor survival outcomes in xenograft models with standard therapies

✓ represent clinical processes of de-differentiation and acquired treatment resistance

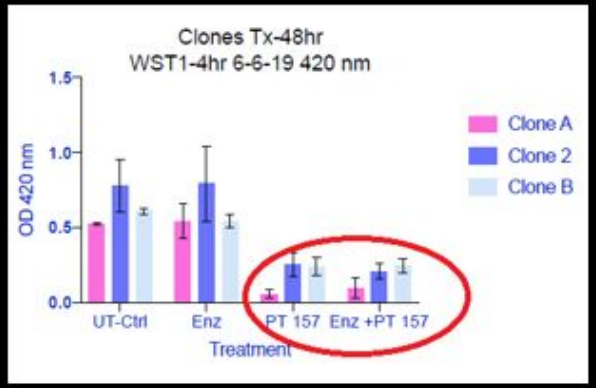
PT vs the clones

PT150 and PT157
vs Drug Resistant Prostate Cancer Clones

Clones A, 2, and B: Derived from a human clinical specimen by spiking the culture with enzalutamide (Enz) for 8 months. The selection pressure produces clones that are particularly aggressive and resistant to therapies, particularly clones A and 2. In xenograft models these tumors grow rapidly and mice die within two days.



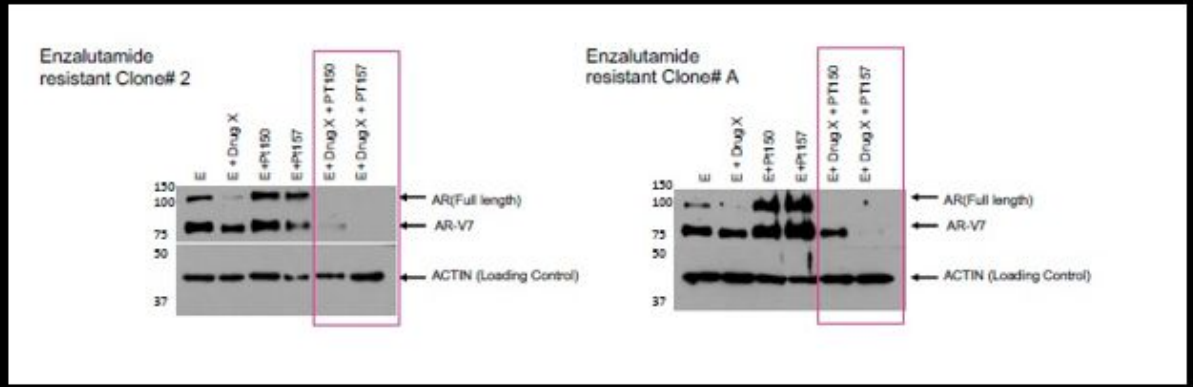
PT150 as single agent outperforms Enzalutamide as single agent



PT157 as single agent outperforms Enzalutamide as single agent

Enzalutamide alone, compared to untreated controls, shows no significant activity against prostate cancer clones A and 2 and borderline activity against clone B. PT-150 and PT157 however show significant efficacy against all 3 clones as a single acting agent and can restore enzalutamide activity in combination therapy.

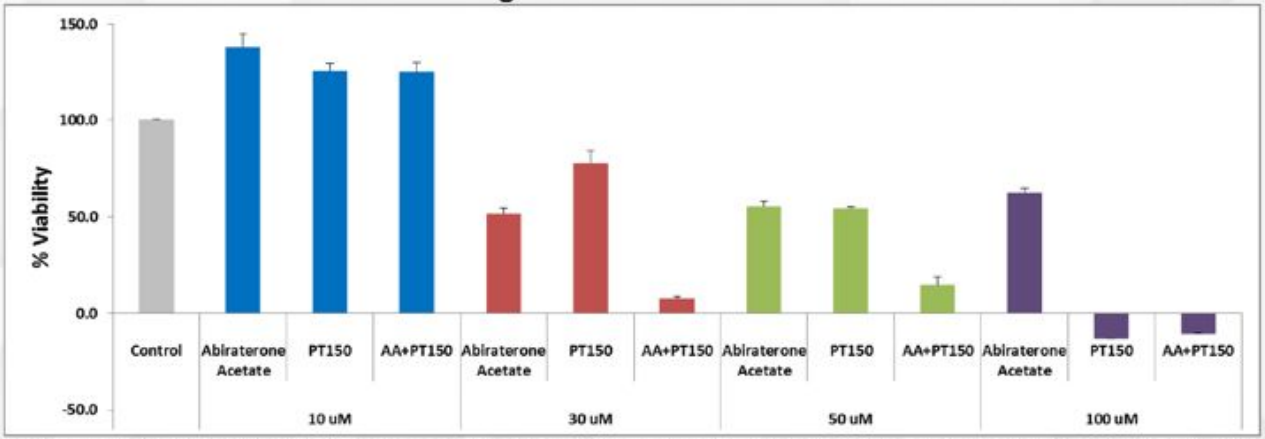
PT drugs- Androgen Receptor Modulation



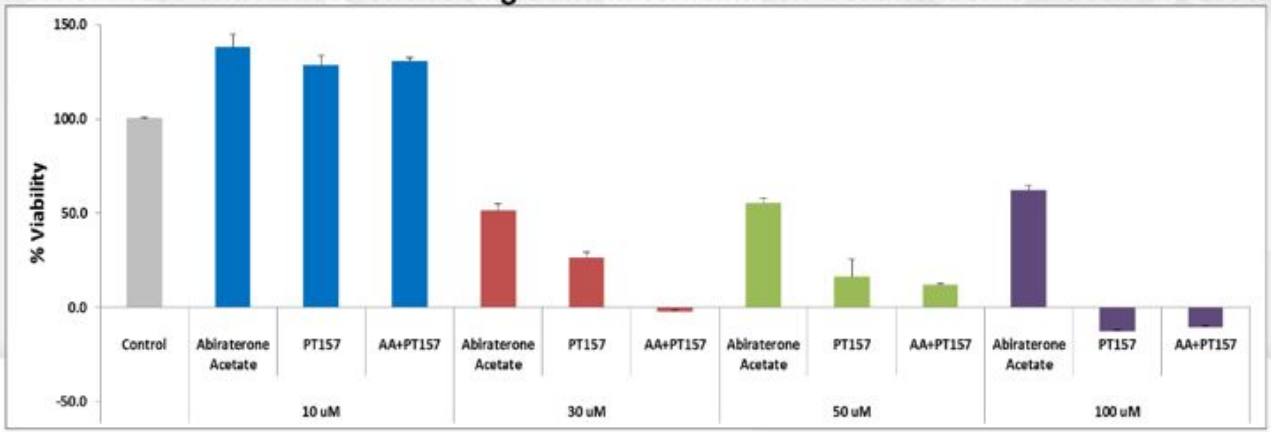
Combination Therapies vs E006AA-hT

E006AA-hT is a highly tumorigenic subline of the primary African-American prostate cancer cell line E006AA that was spontaneously immortalized. E006AA is derived from a 50-year-old African American male patient with organ-confined Gleason 6 tumor.

Effect of PT150 and Abiraterone as single and in combination treatment on CRPC cell line E006AA-hT



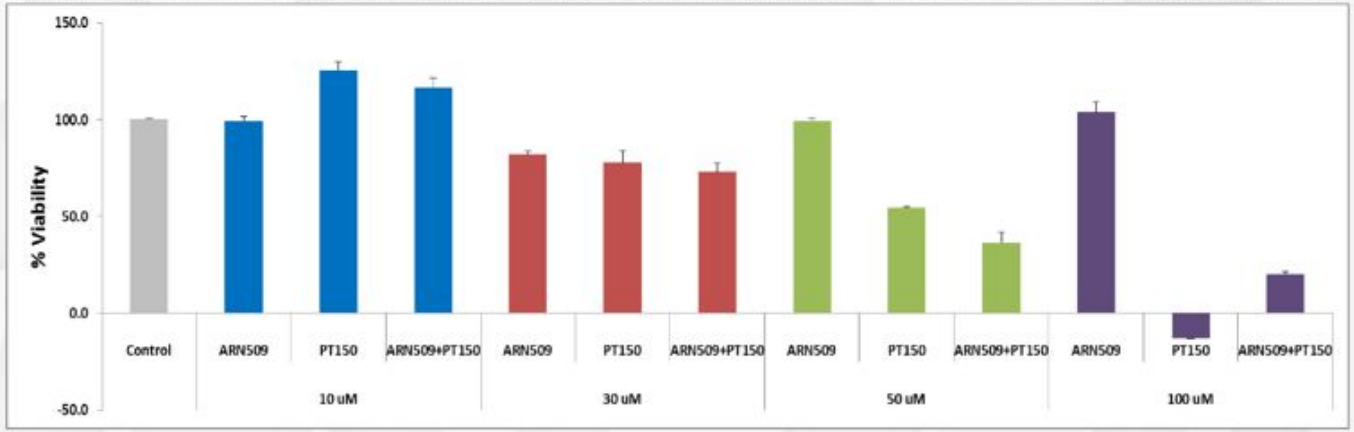
Effect of PT157 and Abiraterone as single and in combination treatment on CRPC cell line E006AA-hT



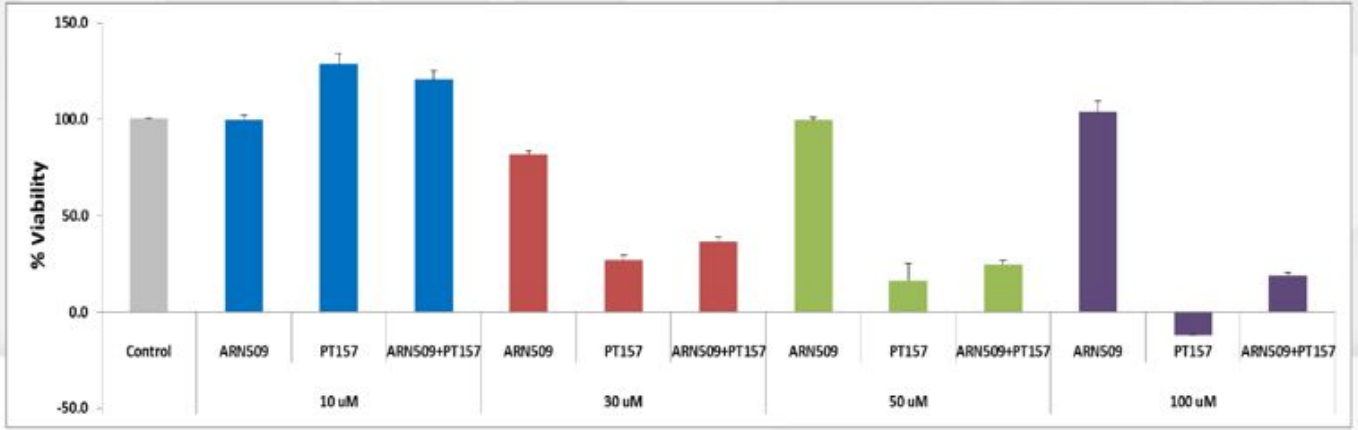
Combination Therapies vs E006AA-hT

E006AA-hT is a highly tumorigenic subline of the primary African-American prostate cancer cell line E006AA that was spontaneously immortalized. E006AA is derived from a 50-year-old African American male patient with organ-confined Gleason 6 tumor.

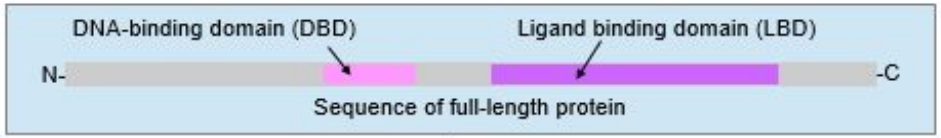
Effect of PT150 and ARN509 as single and in combination treatment on CRPC cell line E006AA-hT

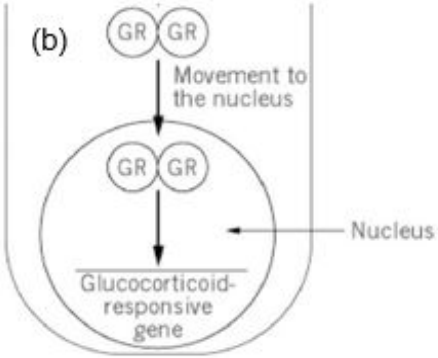


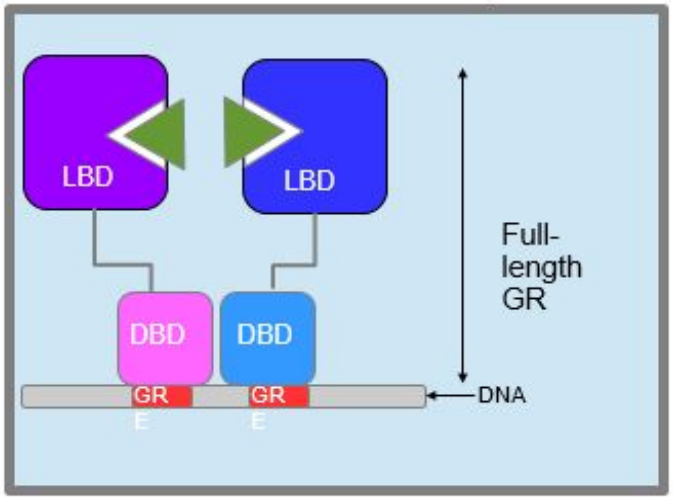
Effect of PT157 and ARN509 as single and in combination treatment on CRPC cell line E006AA-hT



GR dimer interaction with DNA 1/3

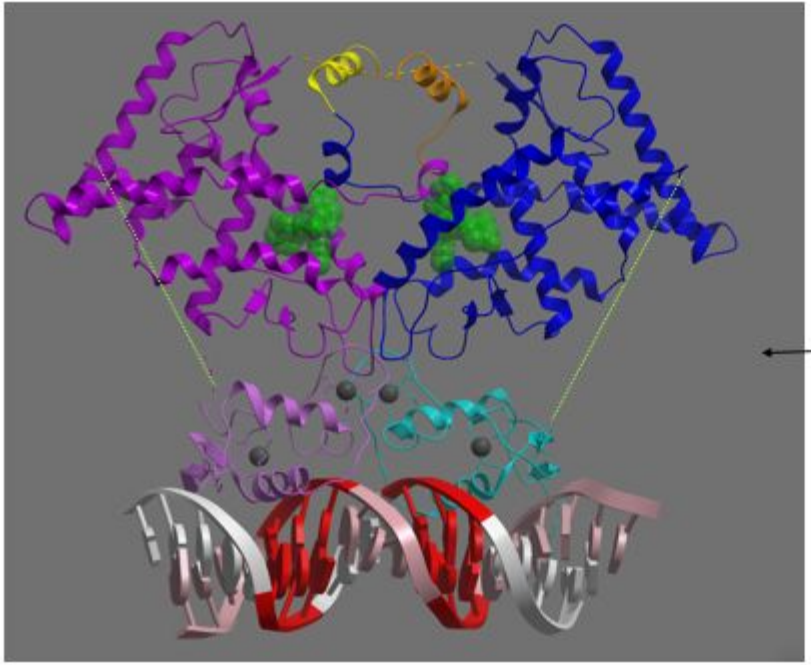


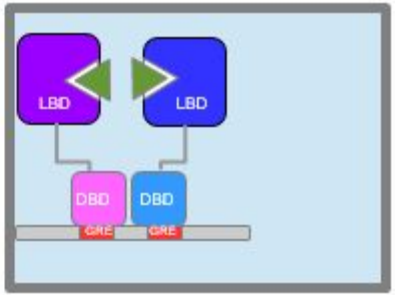




(a) Primary structure of the GR receptor, with the DNA-binding domain (DBD) shown in light purple, the ligand-binding-domain (LBD) in dark purple. N-terminus on left; C-terminus on right. Between the LBD and DBD is an unstructured domain.
(b) cartoon shown earlier of this interaction (taken from slide 1)
(c) Schematic view of DNA-GR dimer interaction. Cartoon, ligand in green, LBD's in dark purple and dark blue, the DBD's in light purple and light blue, the DNA as gray cylinder, and the GRE sequences in red.

Model of GR dimer interaction with DNA 2/3





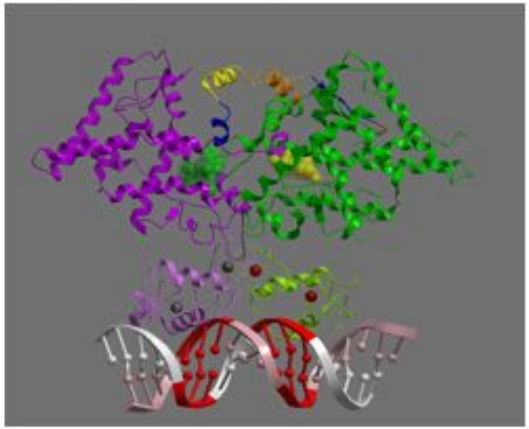
Model of GR dimer bound to DNA. One LBD is dark purple; its DBD is light purple. The other LBD is dark blue; its DBD is light blue. One strand of DNA is pink; the other white. The GRE is shown in red. Gray spheres are zinc atoms (act like zinc fingers). Dashed yellow lines represent unstructured linkers.

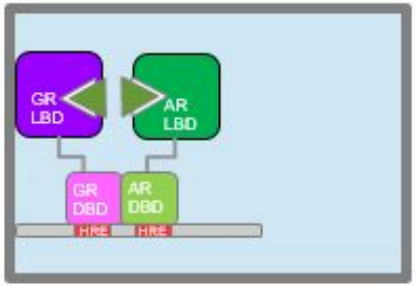
PT150 is shown in green.

Helix 12 of the blue LBD is shown in yellow; for the purple DBD, helix 12 is shown in orange. Note that they intertwine, the yellow helix is closer to the purple LBD than its own LBD (detail on next slide). Model derived from 1NHZ, 1R4R with docking of PT150.

PT-150's anti-tumor effects may be due to GR and AR signaling crosstalk

1. The androgen receptor (AR) plays a central role in prostate cancer.
2. The AR is linked to other cancers, e.g. glioblastoma [1], pancreatic [2], and hepatocellular [2].
3. GR activity contributes to resistance in androgen-resistant prostate cancer [3].
4. Crosstalk between signaling of the glucocorticoid receptor (GR) and the androgen receptor (AR) has long been observed, e.g. GR antagonists modulate AR signaling, and vice versa [4].
5. Both GR and AR bind to similar sequences on DNA - hormone response elements (HRE's). In particular, they both recognize the TGTTCT sequence.
6. As shown on the previous slide, GR functions as a dimer.
7. The formation of GR/AR heterodimers have been reported [4].
8. A model of such a heterodimer can be created, below – nearly identical to the GR homodimer on the previous slide. We hypothesize that PT-150's anti-tumor effects result from its modulation of AR signaling via its antagonism of GR.





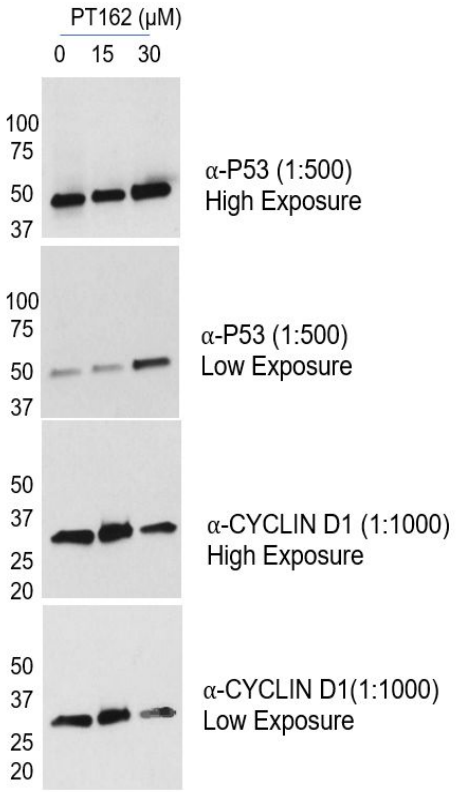
1. Zalcman, et al, Oncotarget, 2018
2. Kanda et al, World J Gastroenterol., 2014
3. Isikbay et al, Hormones & Cancer, 2014
4. Chen et al, JBC, 1997

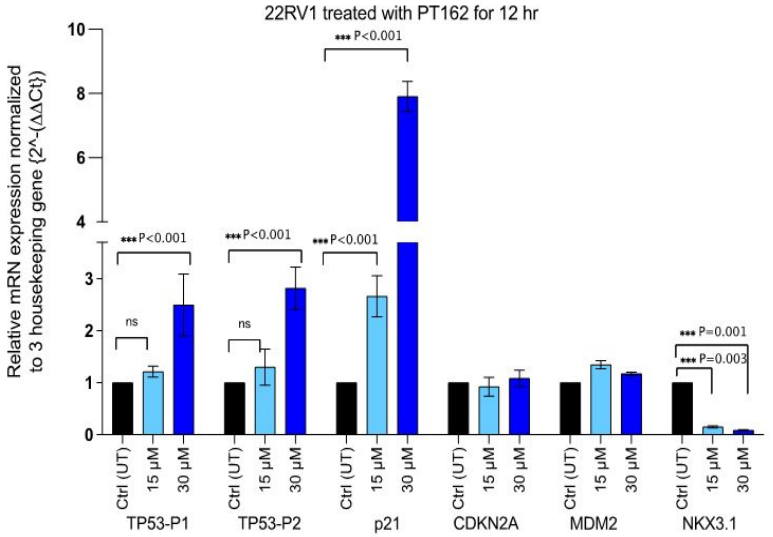
PT162

p53-reactivating cell cycle checkpoint inhibitor, induces cancer cell cycle arrest and/or apoptosis by restoring DNA-binding activity of mutant p53 protein.

PT162

Western blot analysis

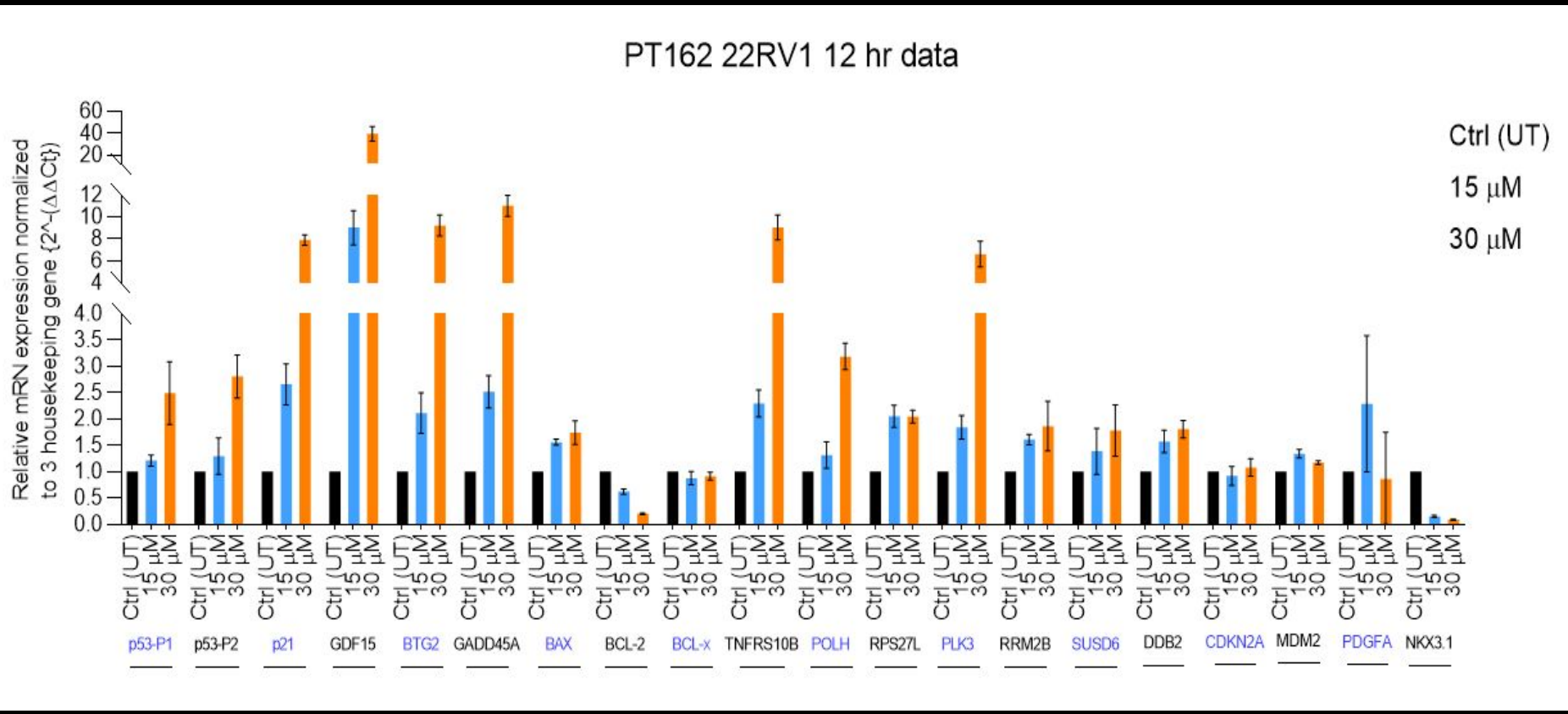


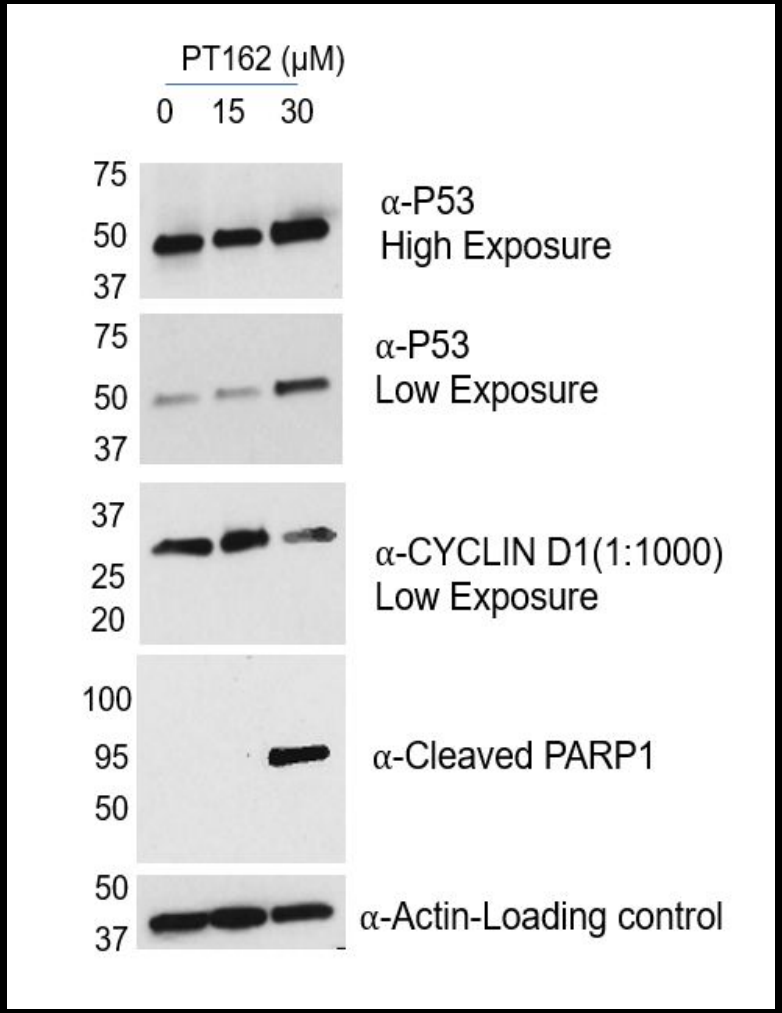


22RV1 cells were treated with PT162 at the indicated concentrations for 12 hr in duplicates. One set was used to analyze protein expression, and the second set was used to analyze RNA using quantitative real-time PCR. Lysates were prepared, and equal protein was analyzed by western blotting. P53 levels were significantly upregulated at 30 µM. Data from high and low exposure blots are provided (Panels A & B). Compare lane 1 (untreated) vs. lane 3 (30 µM). The same blot was probed using CYCLIN D1 antibody, and cyclin D1 levels were found to be downregulated with 30 µM treatment. Data from high and low exposure blots are provided (Panels B & C). Compare lane 1 (untreated) vs lane 3 (30 µM)
TP53 is a tumor suppressor gene, and upregulation of p53 protein levels results in cell cycle arrest and death by downregulating essential cell-cycle proteins like cyclin D1.

We show that PT162 treatment results in upregulation of p53 and consequently downregulation of cyclin D1 levels. Analysis of other downstream signaling molecules of the TP53 pathway is ongoing.

Quantitative RT-PCR
2 µg RNA from control and treated cells were reverse transcribed, and cDNA was used in quantitative real-time PCR analysis. We tested the expression of TP53 using two separate primers (P1 & P2), and 3 genes of the TP53 pathway viz p21, CDKN2A and MDM2. We found that PT162 treatment results in a significant 3-fold upregulation of P53 RNA that correlated with upregulation of p21. However, the levels of CDKN2A and MDM2 were unaffected
Interestingly, the expression of the NKX3.1 gene was significantly downregulated with PT162 treatment. NKX3.1 is a driver of prostate cancer, and the downregulation of NKX3.1 by PT162 further supports its function as an anti-cancer drug.
As mentioned above, we are pursuing these studies further to understand the cellular targets of PT162 using high throughput sequencing methods.


PT162 22RV1 12 hr data
Relative mRN expression normalized to 3 housekeeping gene {2^-(ΔΔCt)}
Ctrl (UT)
15 μM
30 μM
p53-P1
p53-P2
p21
GDF15
BTG2
GADD45A
BAX
BCL-2
BCL-x
TNFRS10B
POLH
RPS27L
PLK3
RRM2B
SUSD6
DDB2
CDKN2A
MDM2
PDGFA
NKX3.1



Quantitative RT-PCR

2 μg RNA from control and treated cells were reverse transcribed, and cDNA was used in quantitative real-time PCR analysis. We tested the expression of TP53 using two separate primers (P1 & P2), and 3 genes of the TP53 pathway viz p21, CDKN2A and MDM2. We found that PT162 treatment results in a significant 3-fold upregulation of P53 RNA that correlated with upregulation of p21 and canonical p53 targets, including GD15 (40 fold), BTG2 (10 fold), GADD45 (11 fold), Bax (2 fold), TNFRSF10 B (8 fold). As expected BCL-2 expression was downregulated. Upregulation of Bax and downregulation of BCL-2 is consistent with pro-optotic changes.

Interestingly, the expression of the NKX3.1 gene was significantly downregulated with PT162 treatment. NKX3.1 is a driver of prostate cancer, and the downregulation of NKX3.1 by PT162 further supports its function as an anti-cancer drug.

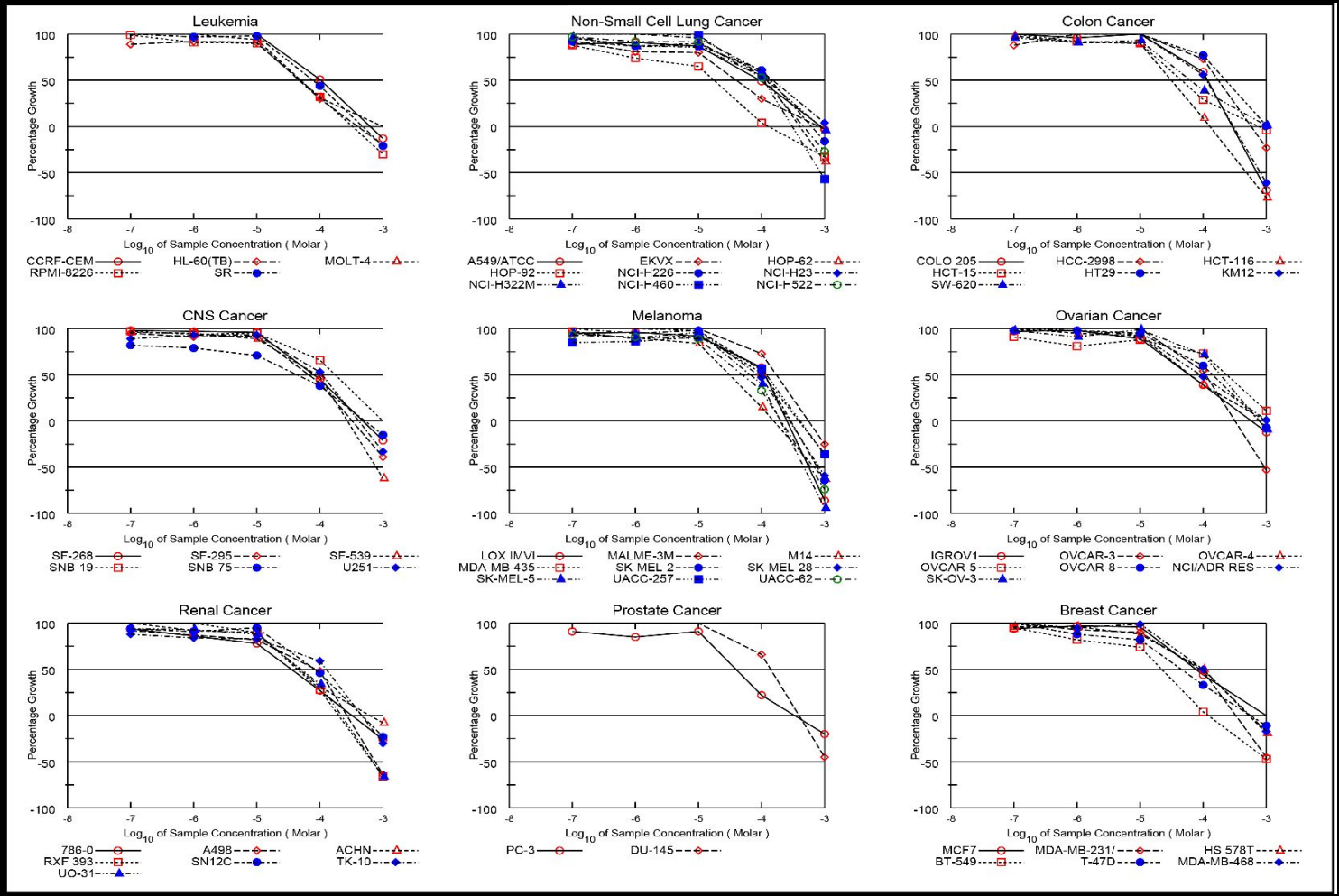
As mentioned above, we are pursuing these studies further to understand the cellular targets of PT162 using high throughput sequencing methods.

Additional oncology data available upon request:

- Triple Negative Breast Cancer
- Ovarian Cancer
- Glioblastoma Brain Cancer
- Liver Cancer
- Pancreatic Cancer
- Multiple Myeloma

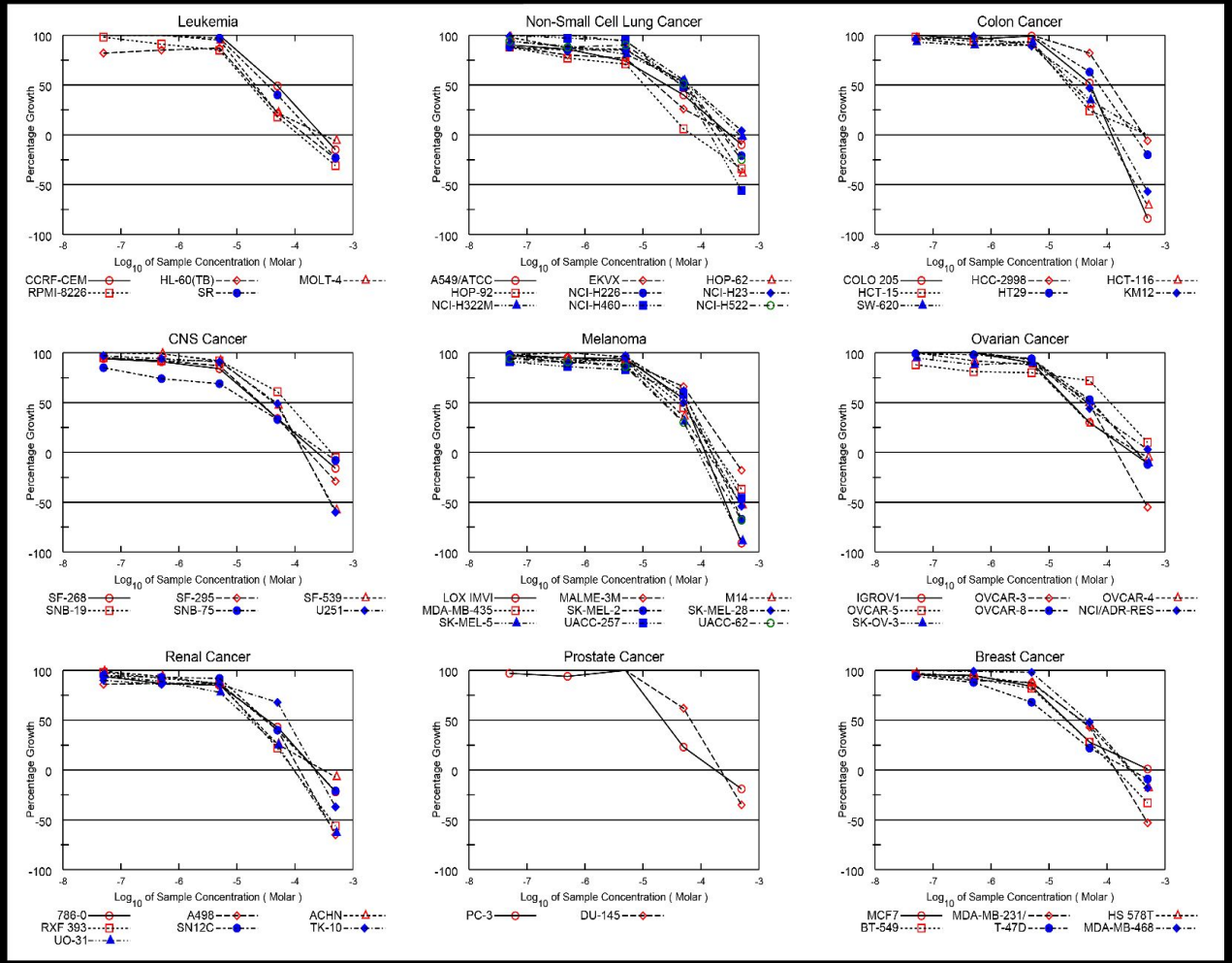
National Cancer Institute

PT150 Dose Response Curves



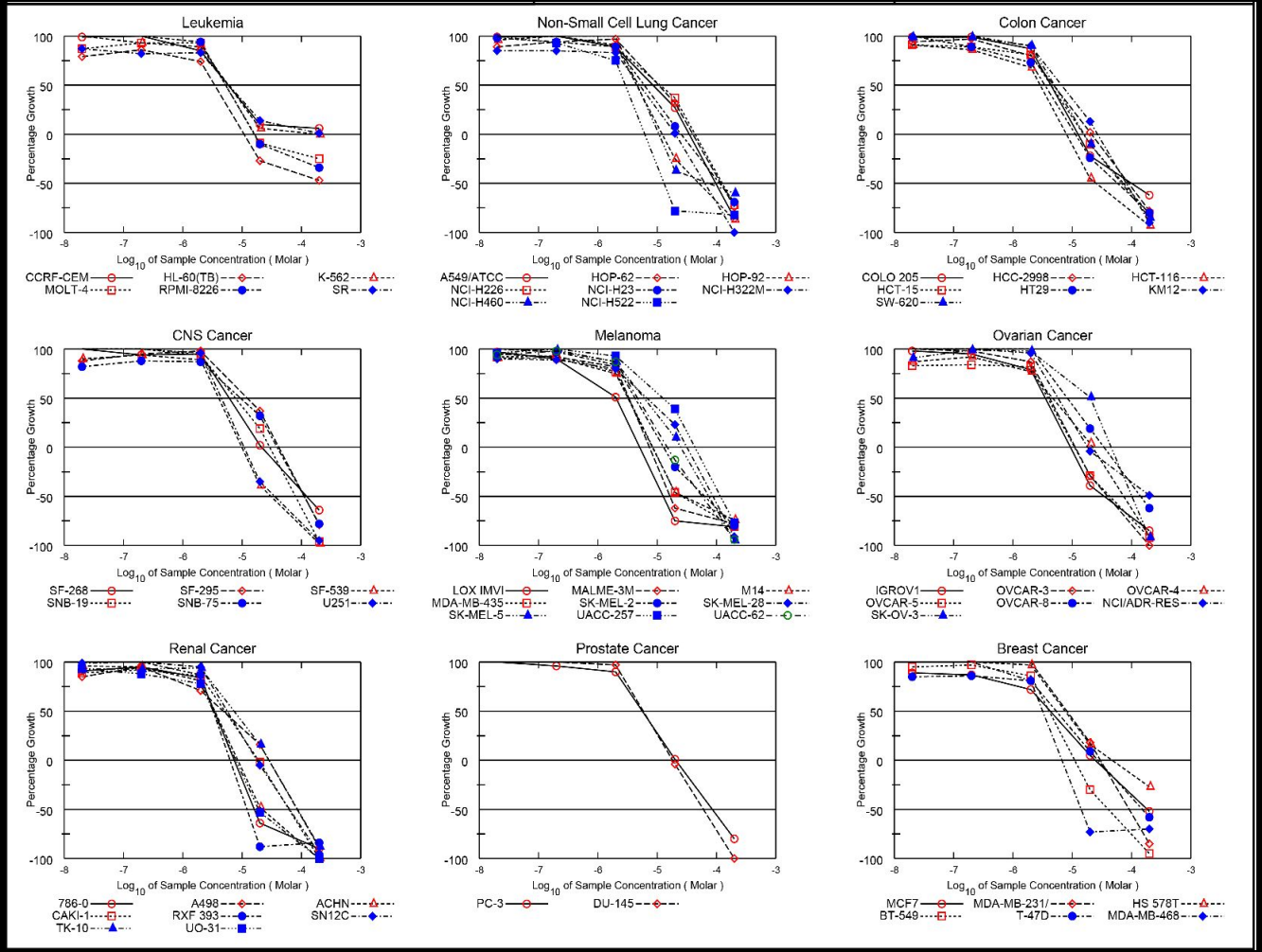
National Cancer Institute

PT157 Dose Response Curves



National Cancer Institute

PT162 Dose Response Curves

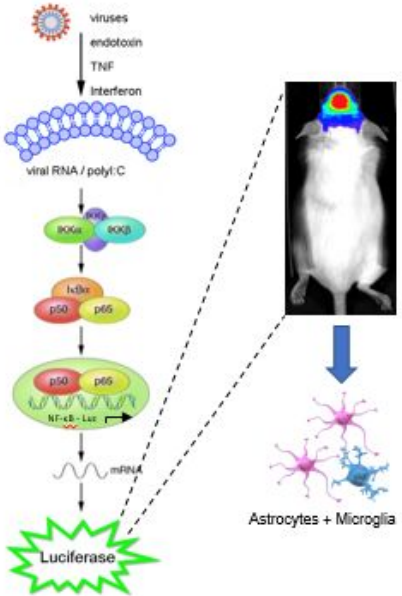


THERAPEUTICS

Neuroinflammation

- **PT150 directly prevents activation of inflammatory signaling pathways in microglia and astrocytes in response to diverse activators of innate immunity**
- **Orally delivered PT150 reduces neuroinflammation in the brains of Syrian hamsters infected with SARS-CoV-2, as well as inhibiting expression of inflammatory genes in lung**
- **PT150 effectively reduces activation of microglia and astrocytes in multiple brain regions in rats exposed to fentanyl**
- **In vivo neuroprotective effect of PT150 in the rotenone model of Alzheimer's/Parkinson's disease**
- **PT150 effectively inhibits neuroinflammation in multiple cellular and animal models of inflammatory brain injury, as well as increasing cognitive performance.**
- **The efficacy of PT150 across different species and in different models underscores the pharmacodynamic potency in preventing neuroinflammation.**

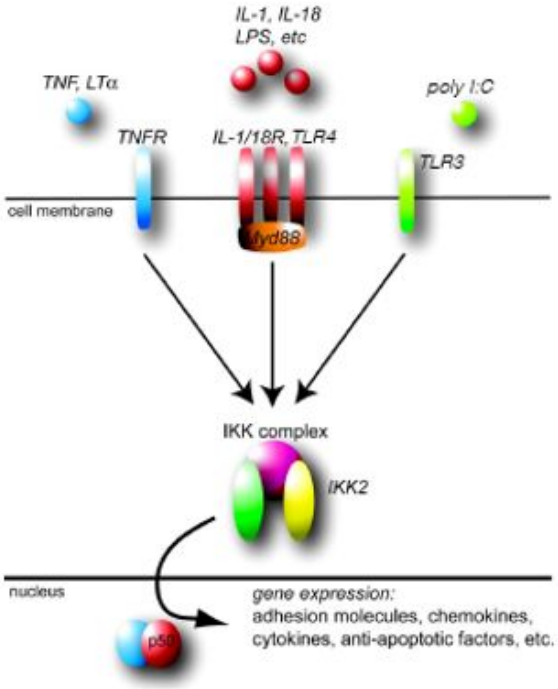
PT150 compounds suppress neuroinflammation in primary brain glial cells

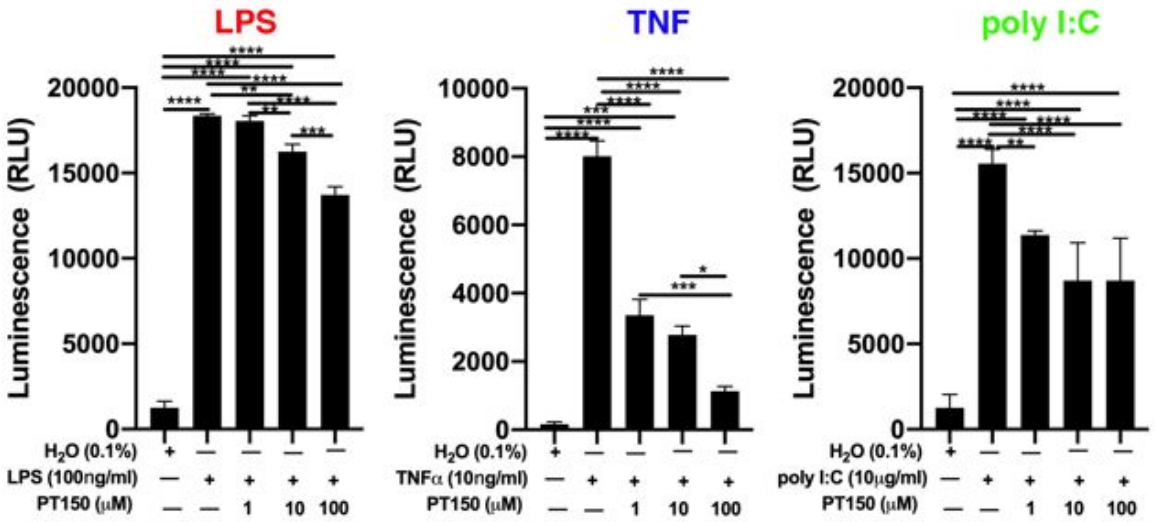


Astrocytes + Microglia

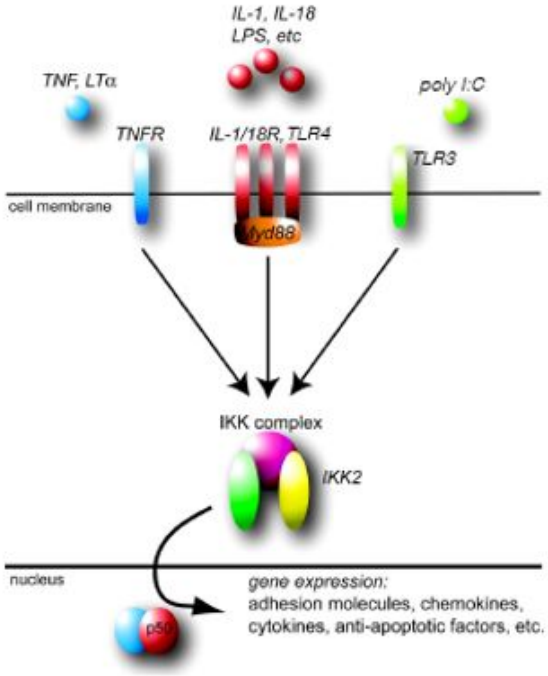
- Mixed cultures of primary astrocytes and microglia were isolated from NF-kappaB-Luciferase reporter mice
- Cells were treated with three different inducers of inflammation: poly I:C (a mimic of viral RNA), LPS (a bacterial cell wall component) or Tumor Necrosis Factor (TNF)
- Dose-dependent suppression of inflammation was seen with different PT150 analogs and TPR1.

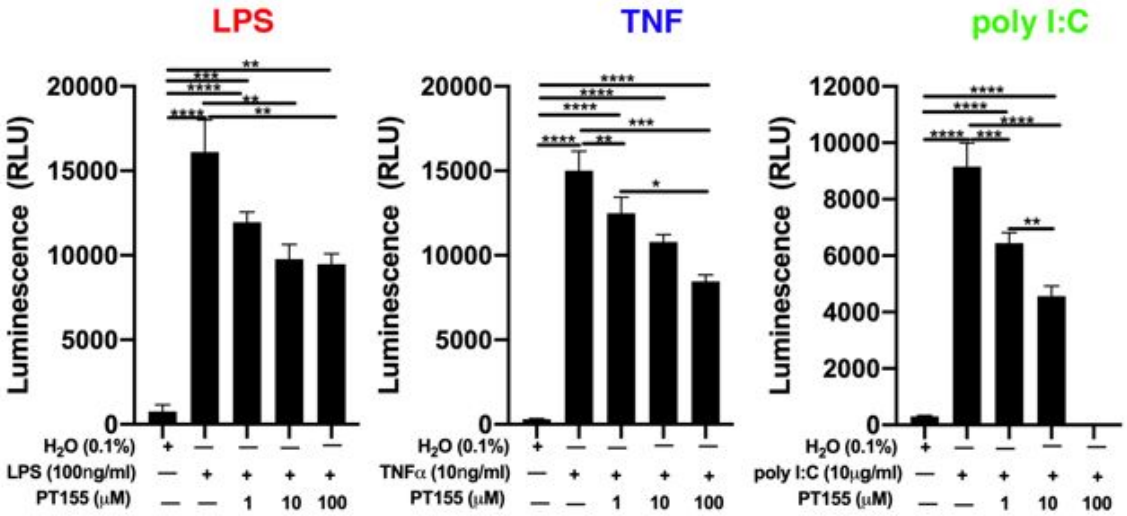
Inhibition of neuroinflammation: PT150



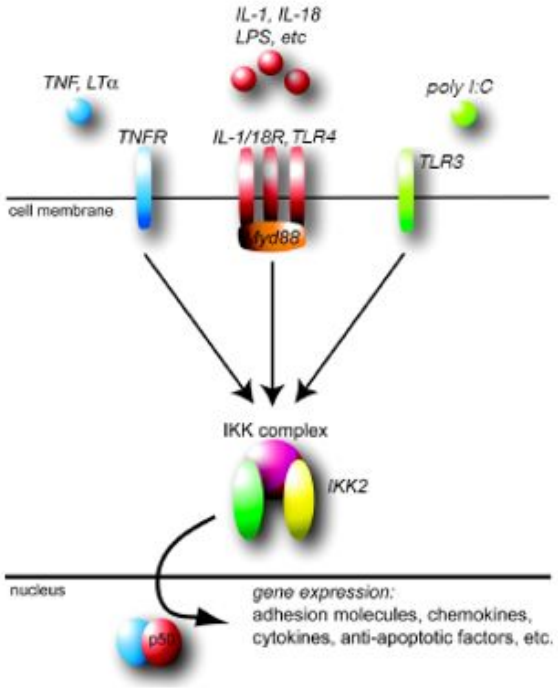


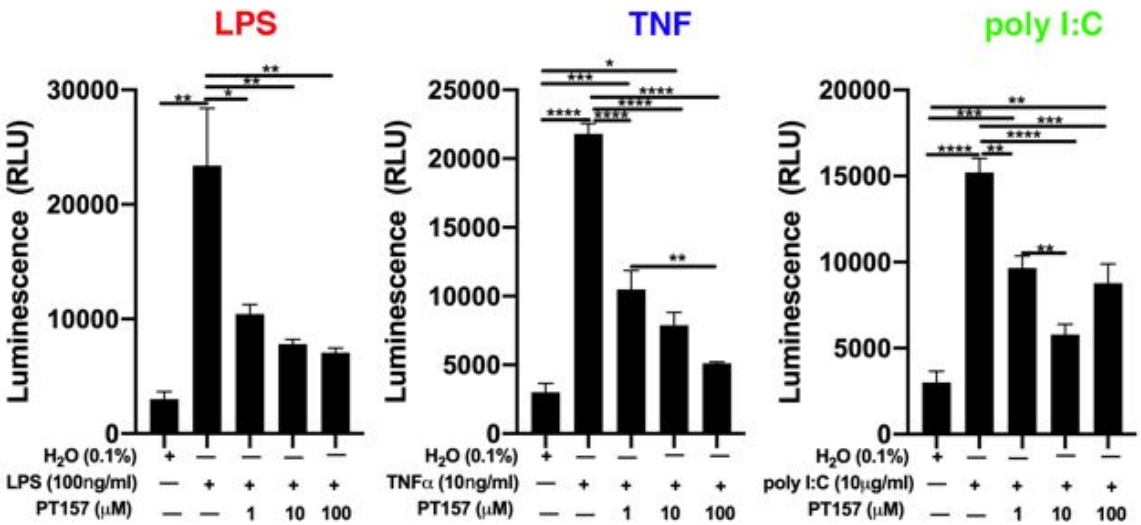
Inhibition of neuroinflammation: PT155



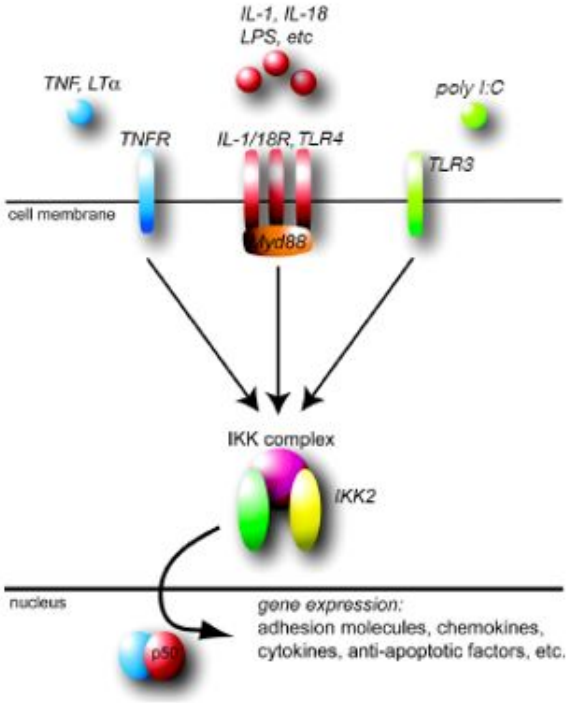


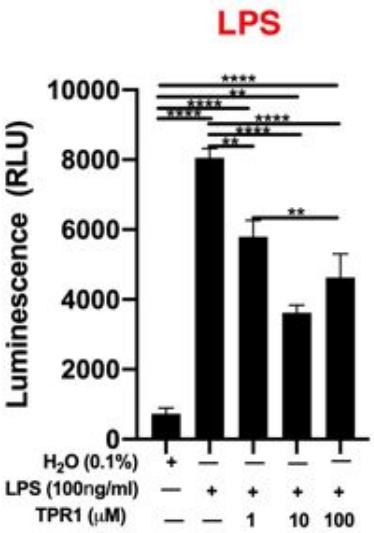
Inhibition of neuroinflammation: PT157

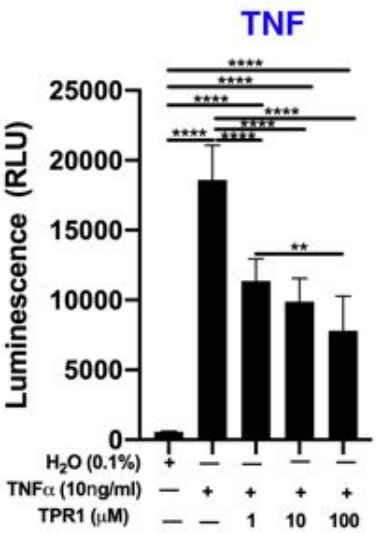


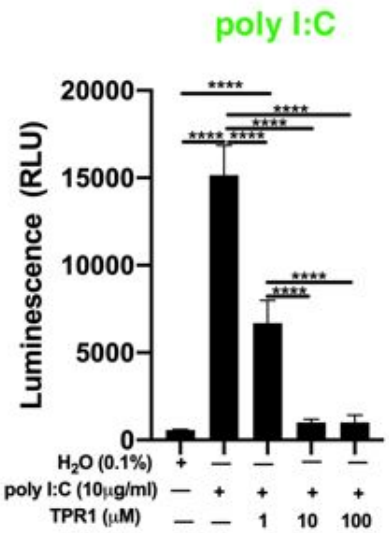


Inhibition of neuroinflammation: TPR1

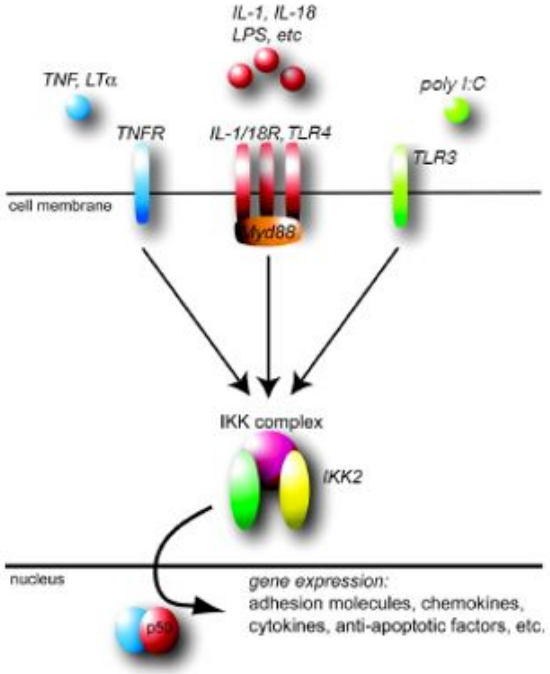


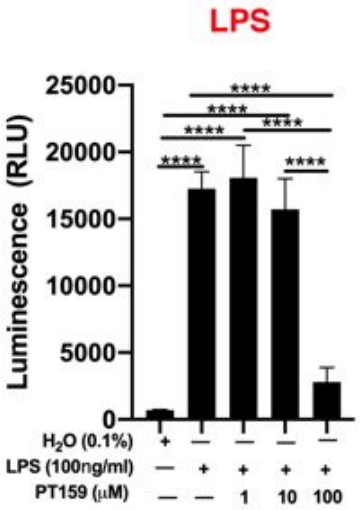


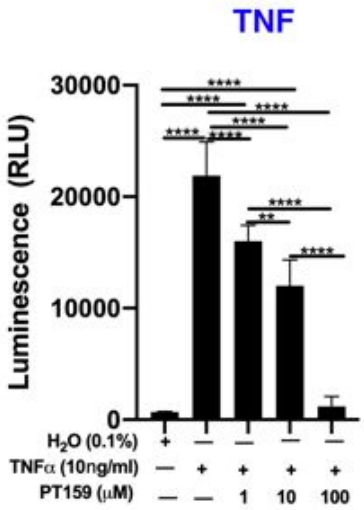


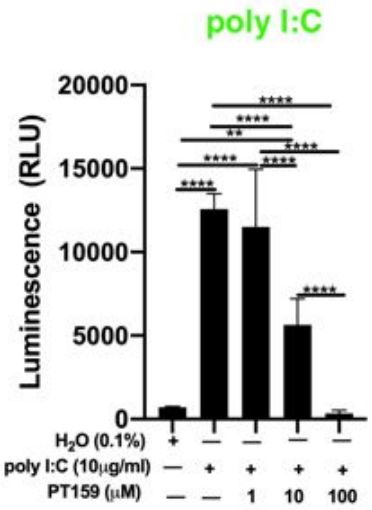


Inhibition of neuroinflammation: PT159 (TPR-1 + PT150)

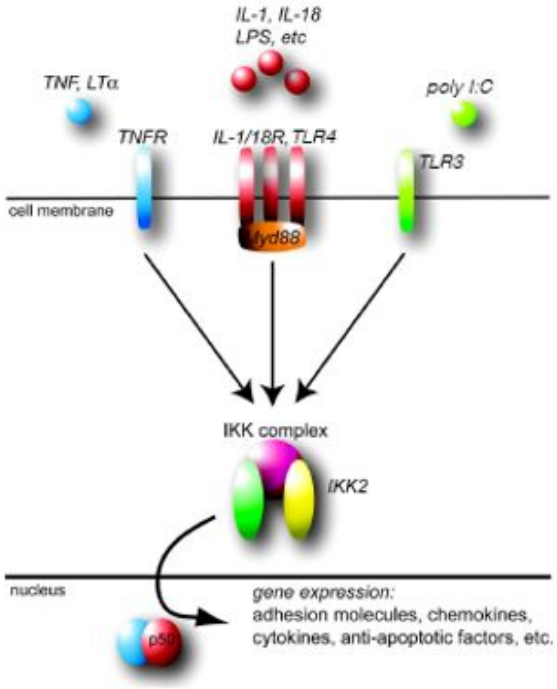


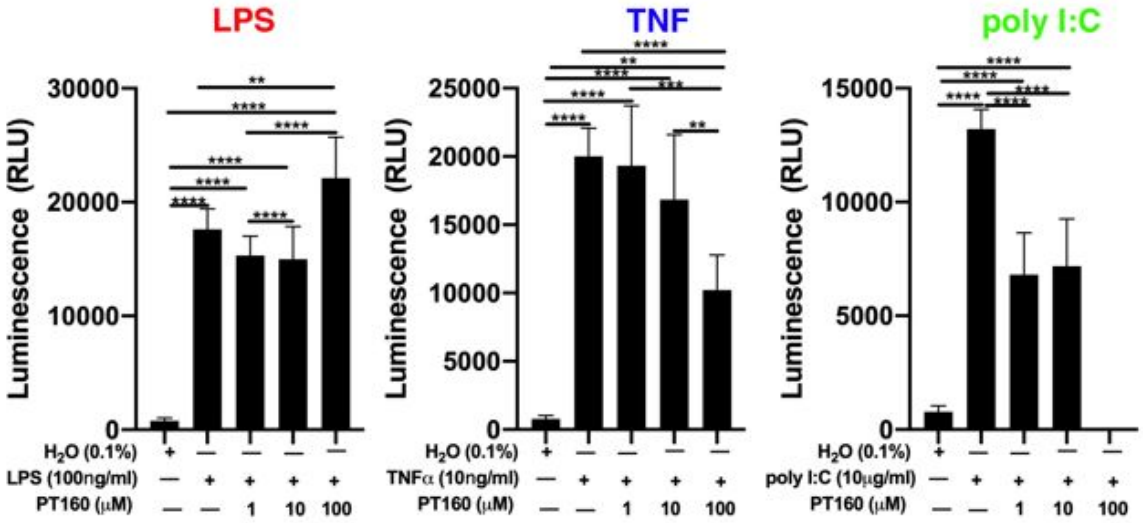




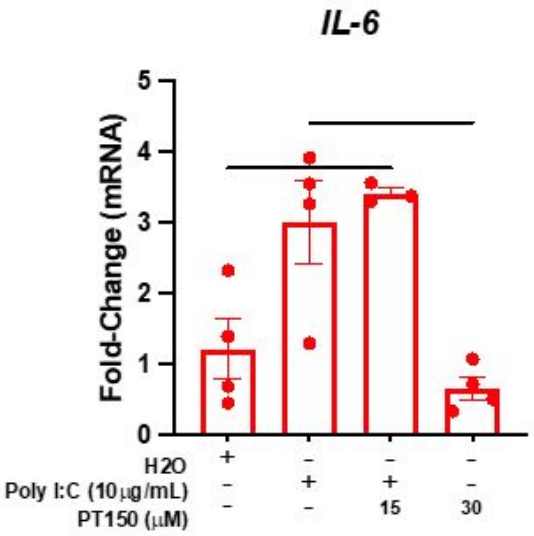


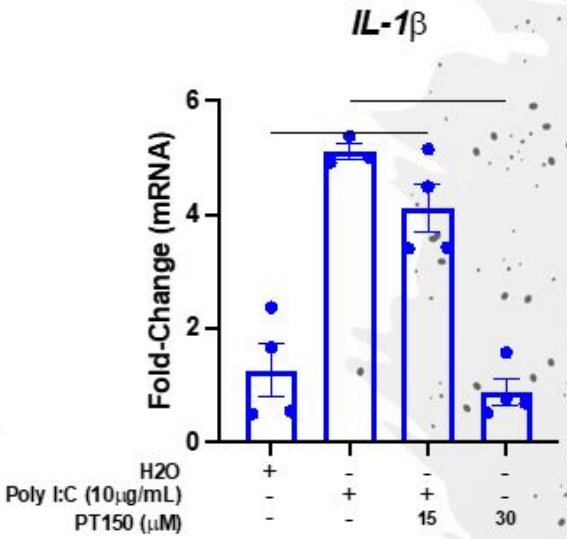
Inhibition of neuroinflammation: PT160 (TPR-1 + PT155)

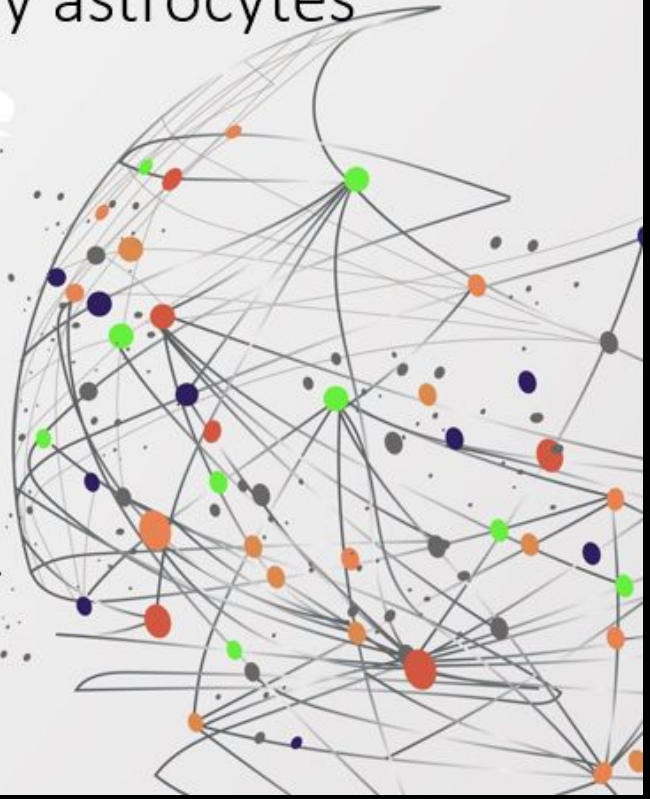




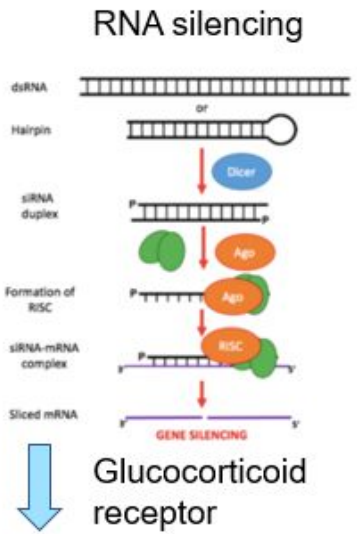
PT150 decreases expression of the inflammatory cytokines IL-6 and IL-1β in primary astrocytes

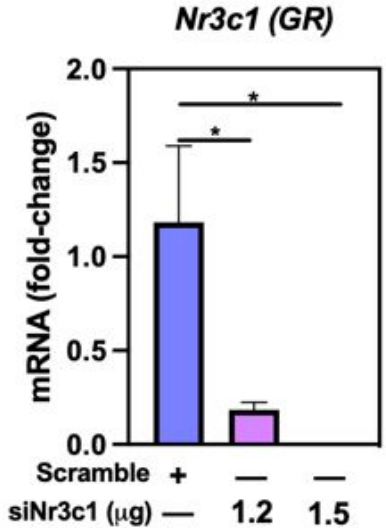


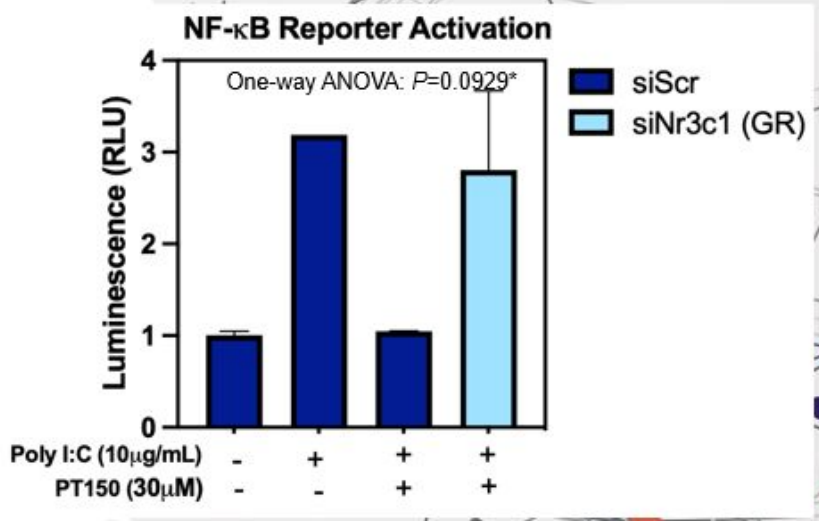




RNA silencing of GR expression blocks the anti-inflammatory activity of PT150 in primary astrocytes

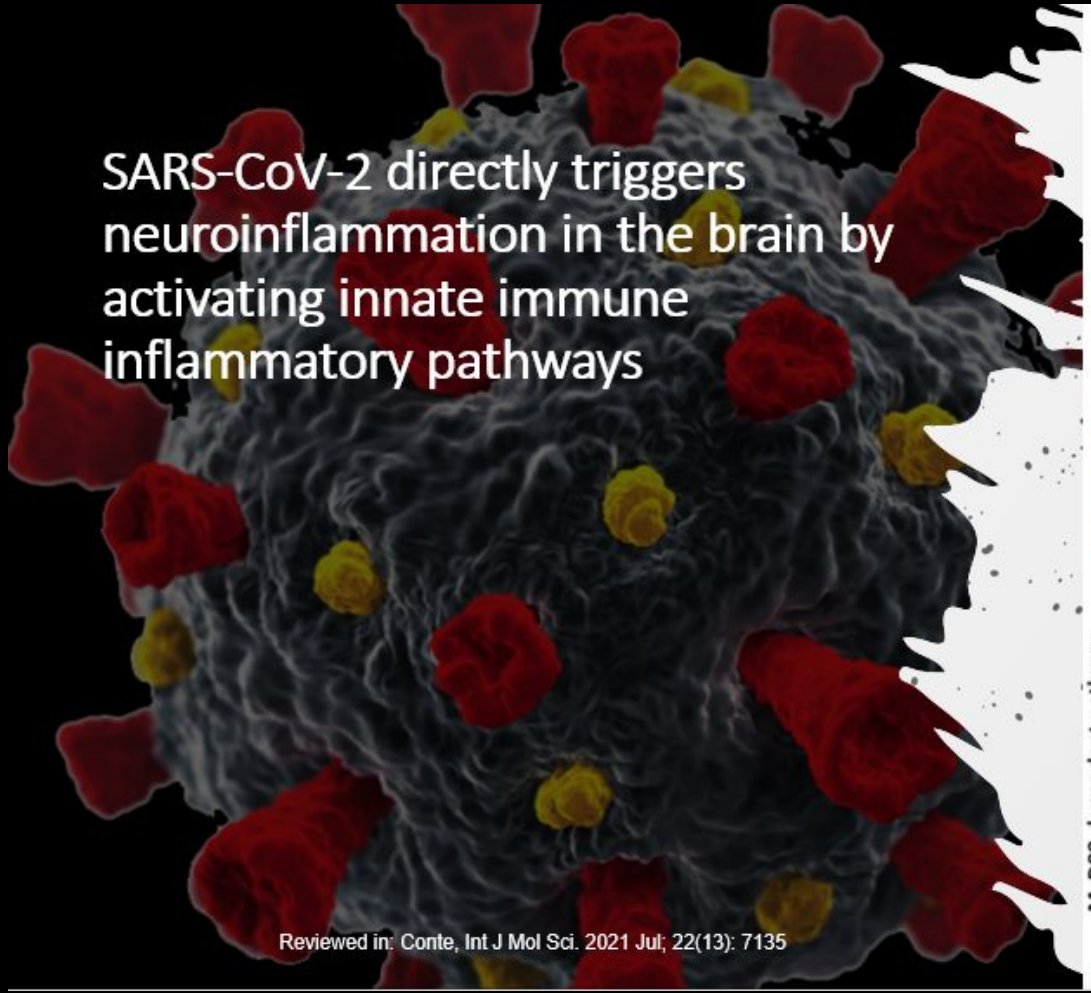


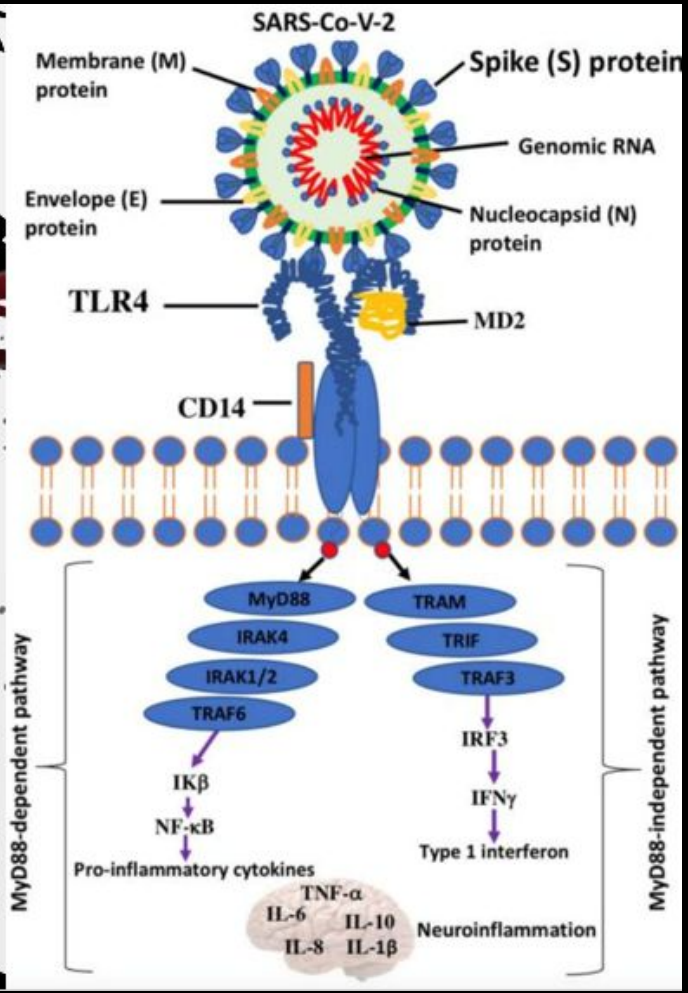




*Preliminary experiment: *N*=4 biological replicates per group

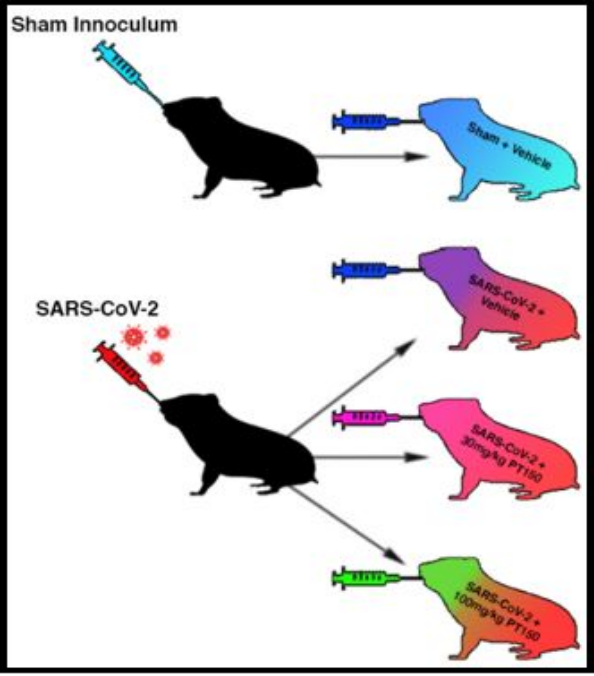
SARS-CoV-2 directly triggers neuroinflammation in the brain by activating innate immune inflammatory pathways





Reviewed in: Conte, Int J Mol Sci. 2021 Jul; 22(13): 7135

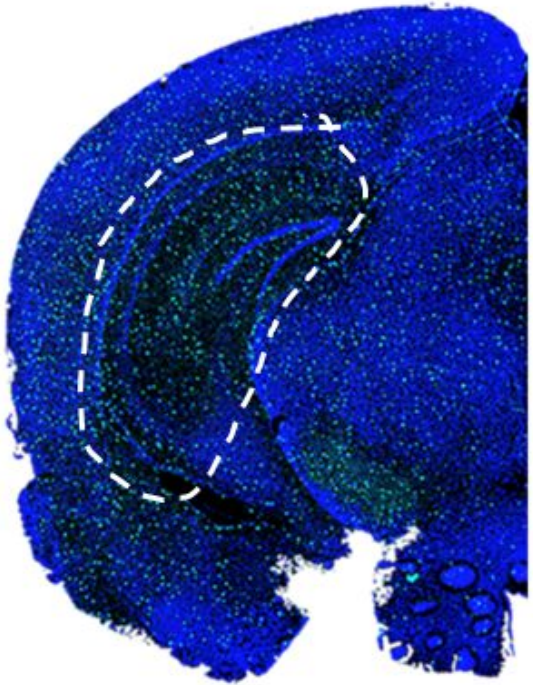
Summary:
Pre-clinical in vivo studies of PT150 for SARS-CoV-2 infection in Syrian golden hamsters

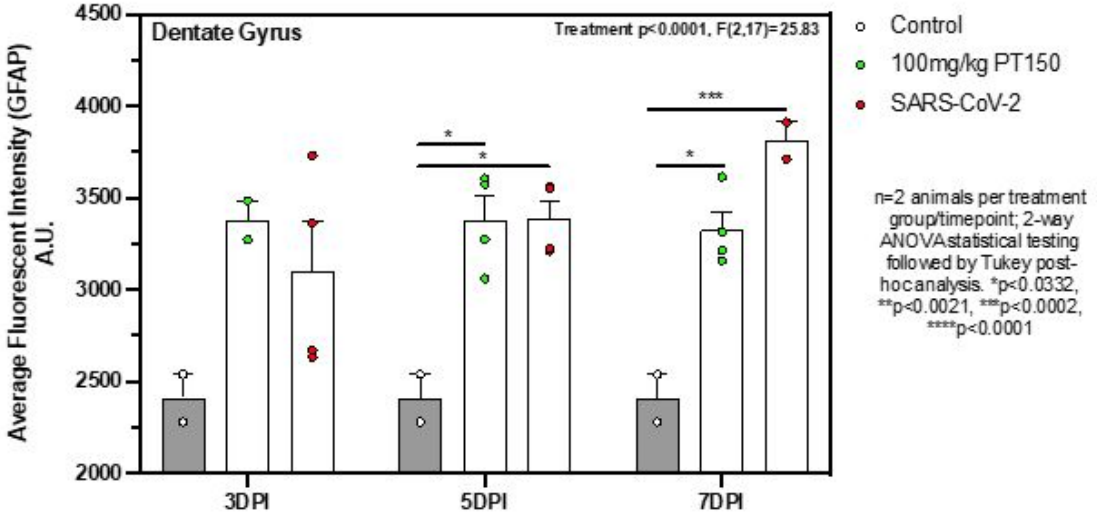


Day 3, Day 5, Day 7

- Viral titers
- Viral and host RNA analysis
- Histopathology

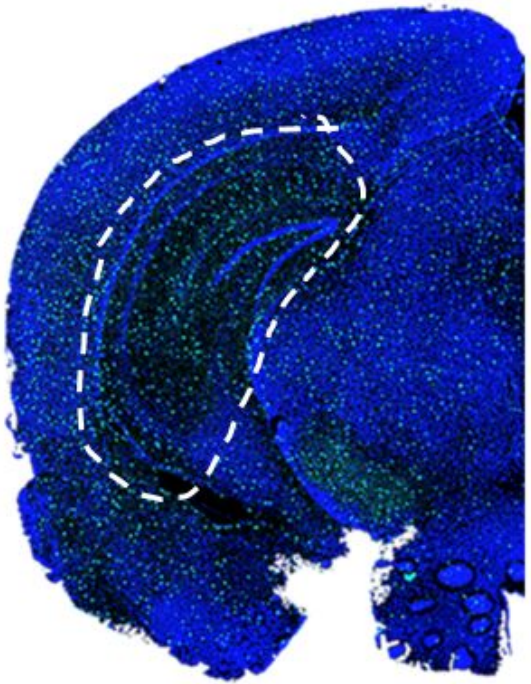
PT150 *decreases astrogliosis* in the hippocampus following SARS-CoV-2 infection

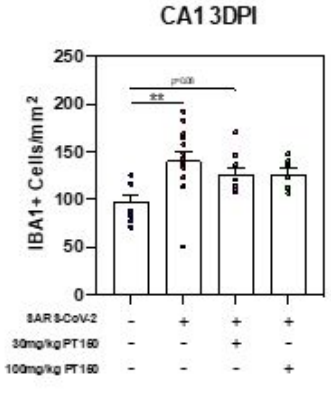


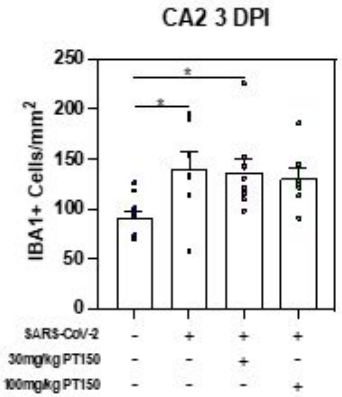


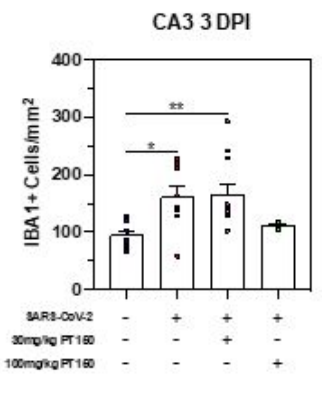
n=2 animals per treatment group/timepoint; 2-way ANOVA statistical testing followed by Tukey post-hoc analysis. *p<0.0332, **p<0.0021, ***p<0.0002, ****p<0.0001

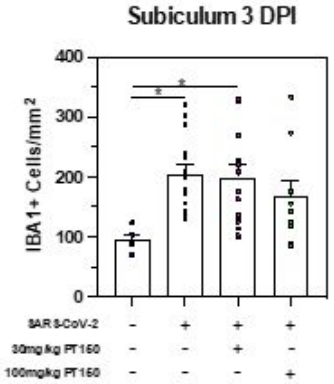
PT150 *decreases microgliosis* in multiple regions of the hippocampus following SARS-CoV-2 infection

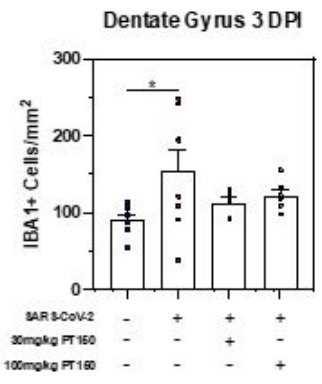








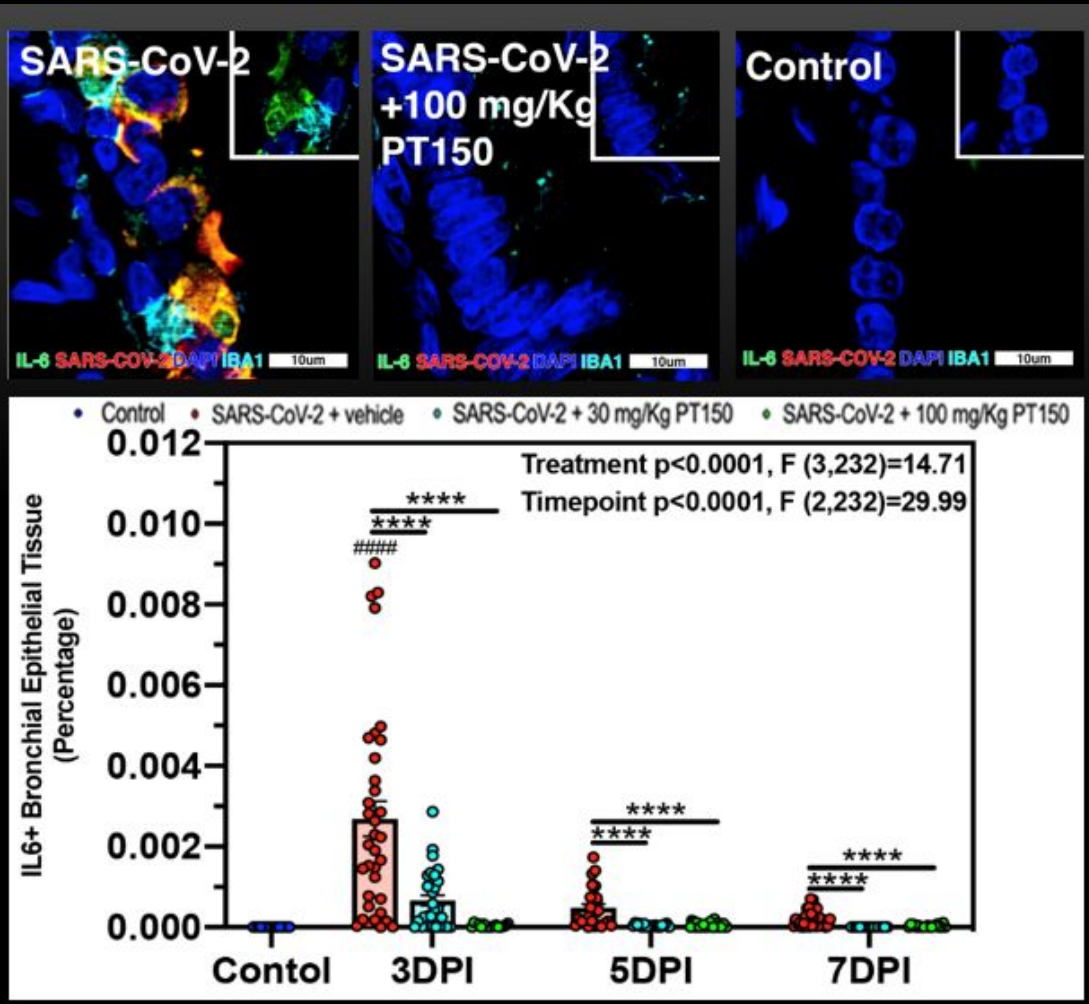




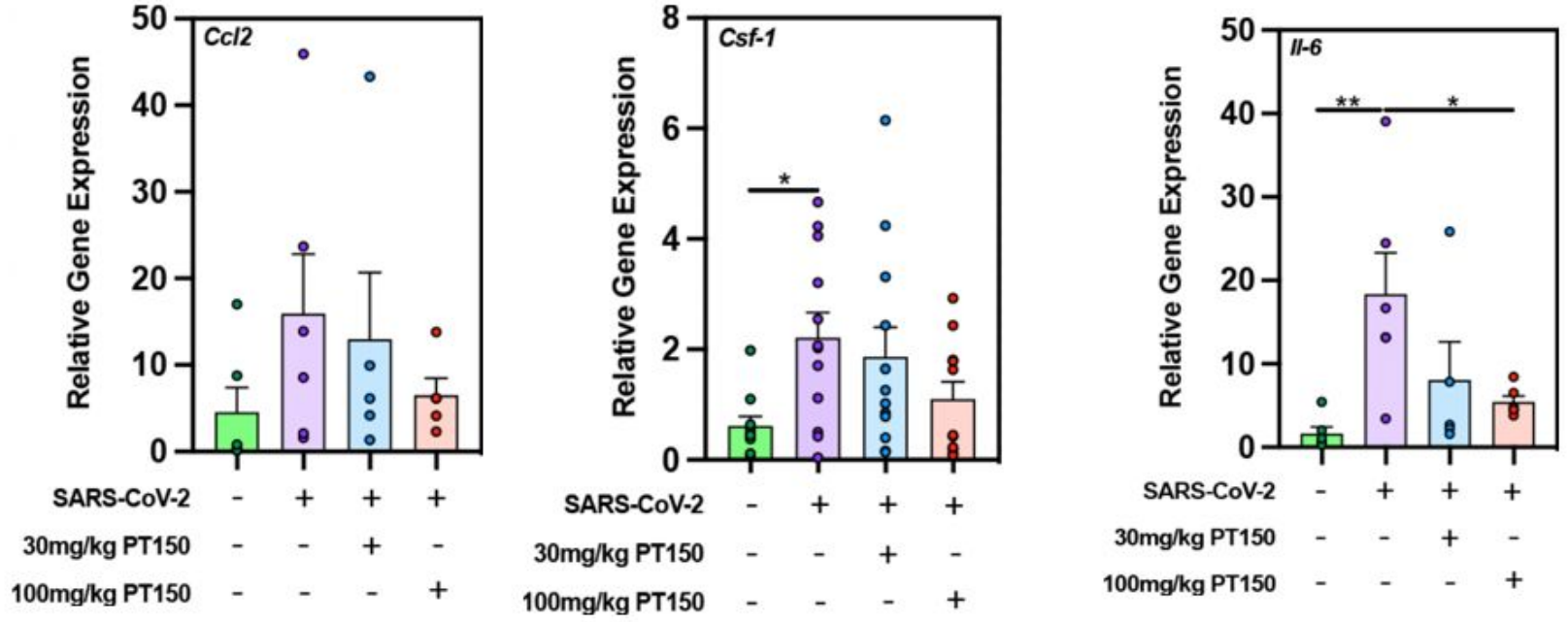
Evidence of anti-inflammatory/immunomodulatory activity of PT150 *in vivo*: treatment decreases protein levels of the inflammatory cytokine Interleukin-6 (IL-6) in lung following infection with SARS-CoV-2

IL-6 produced by activated macrophages is known to be a critical mediator of lung injury in COVID-19 patients.

In Syrian golden hamsters infected with SARS-CoV-2, there was *a significant decrease in expression of IL-6* in the bronchiolar epithelial cell layer at all timepoints in the lungs of animals given PT150 at 30 and 100 mg/Kg/day.

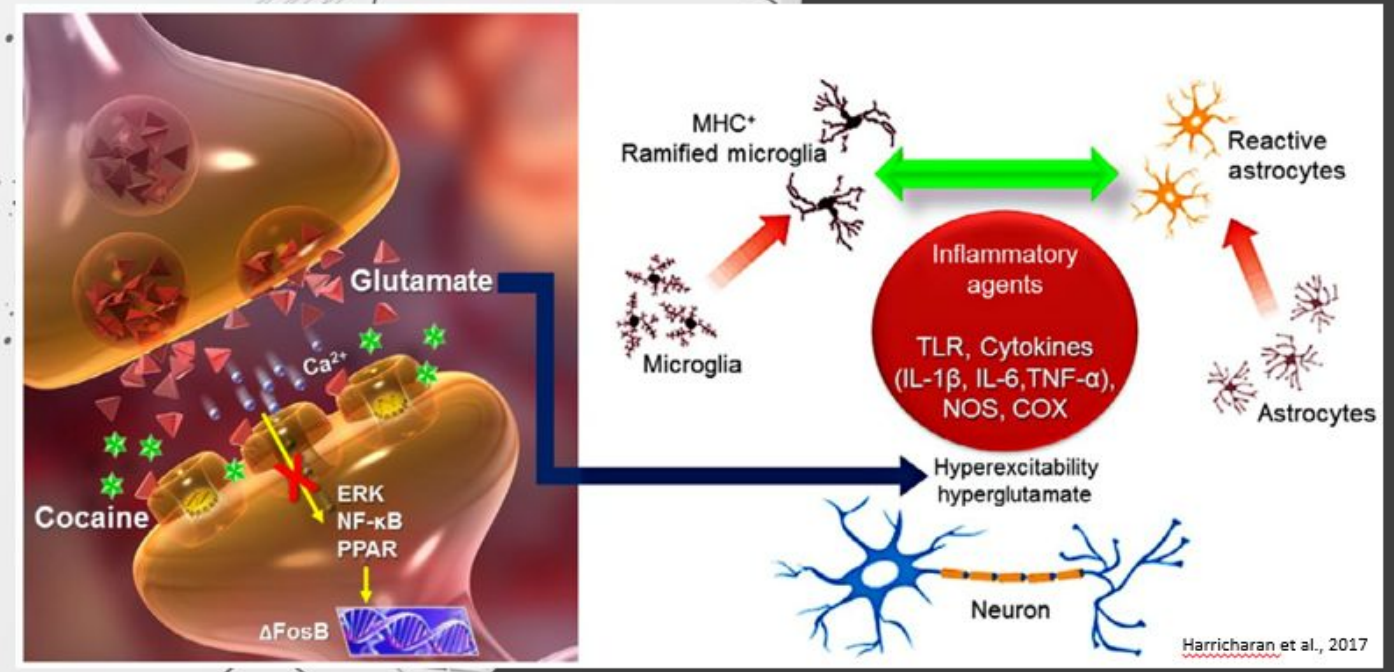


Additional *in vivo* evidence of anti-inflammatory activity: PT150 decreases mRNA expression inflammatory cytokines in lung following infection with SARS-CoV-2

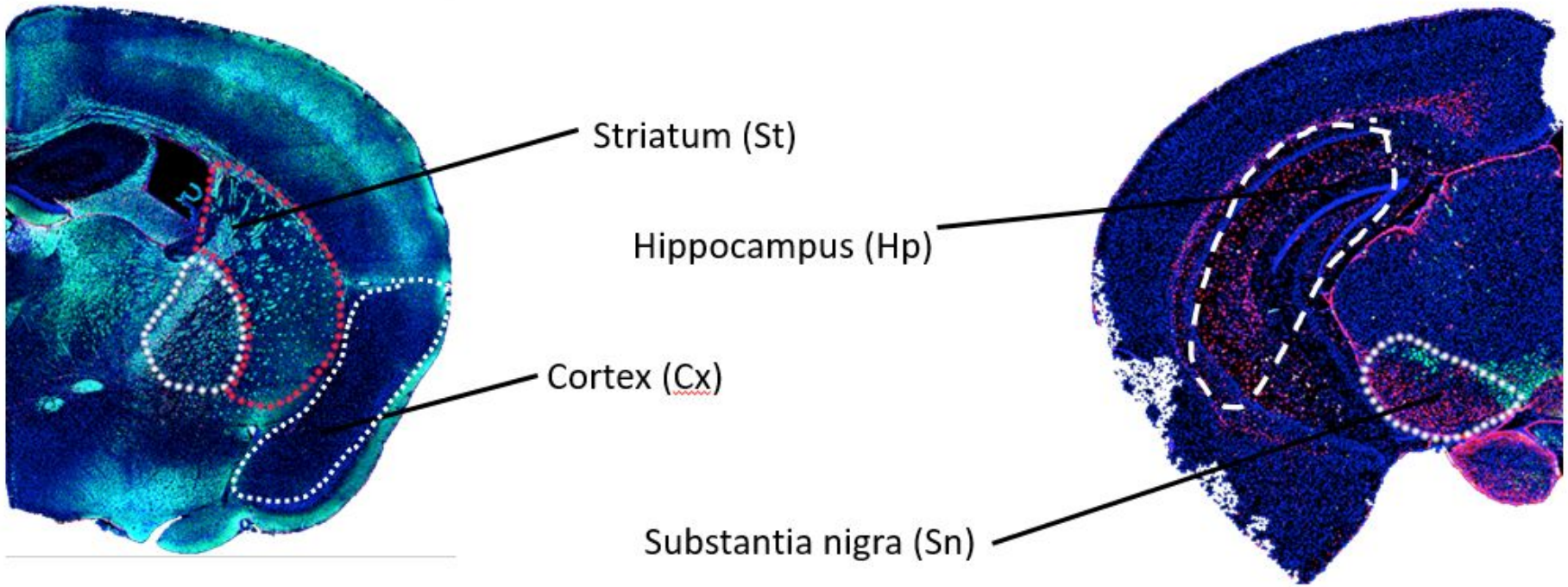


Anti-neuroinflammatory effects of PT150 in the rat model of fentanyl addiction

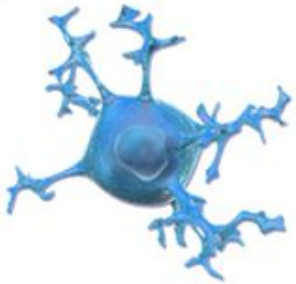
Neuroinflammation is an important aspect of addiction

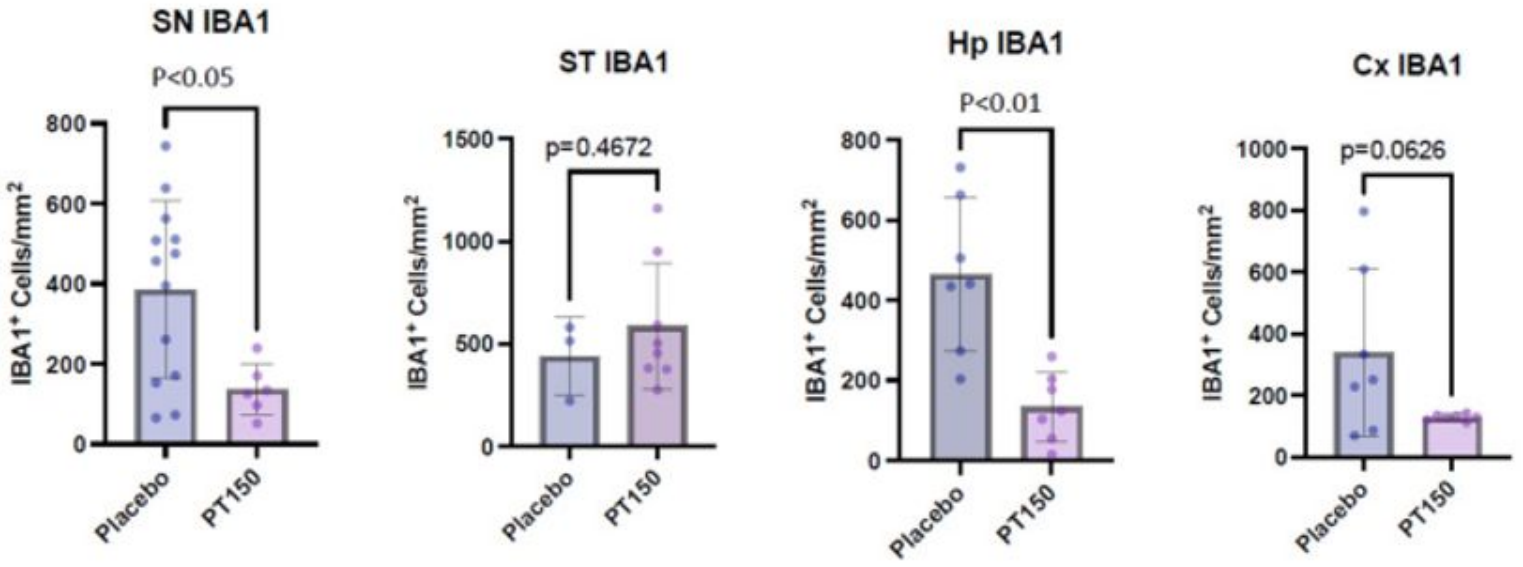


Brain regions evaluated for gliosis in fentanyl-treated rats given placebo or PT150

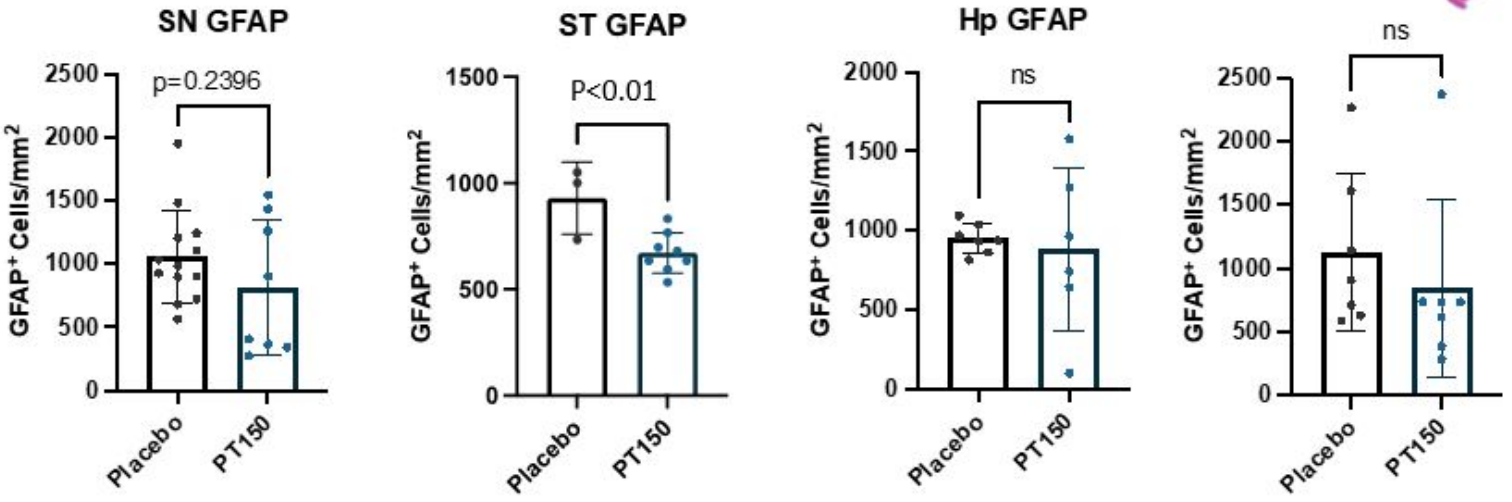


PT150 *reduces microgliosis* in fentanyl-treated rats

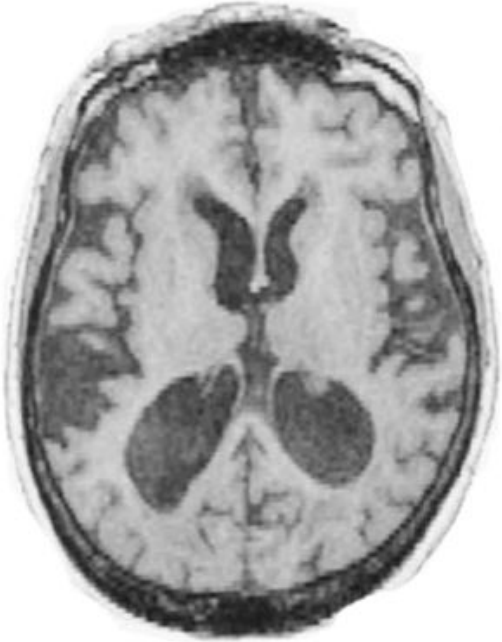


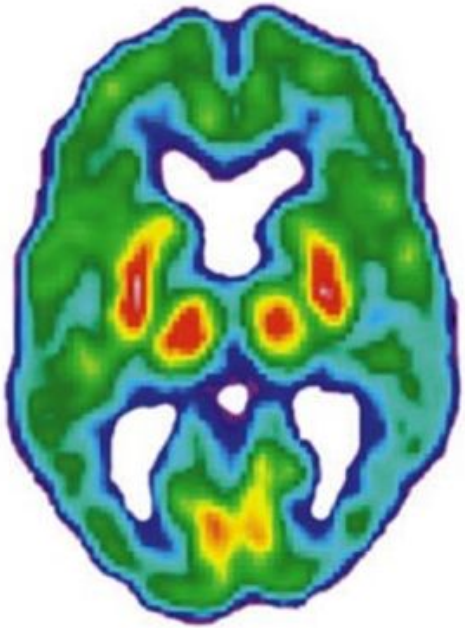


PT150 *reduces astrogliosis* in fentanyl-treated rats



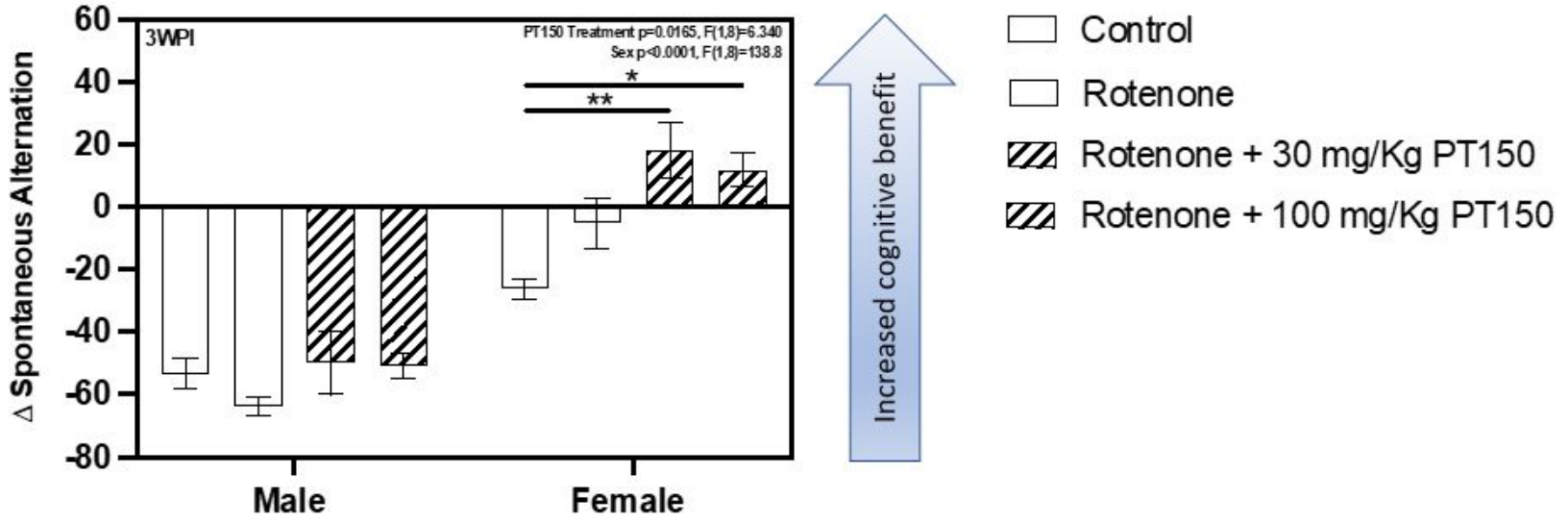
Both Alzheimer's and Parkinson's disease are characterized by metabolic deficits resulting in brain atrophy that result in degradation of cognitive and motor function





- Rotenone is a naturally occurring pesticide and mitochondrial inhibitor used to model brain dysfunction in Parkinson's disease and related neurodegenerative disorders (Rocha and Tjalkens et al., *Neurobiology of Disease*, 167; 2022)
- Studies were designed to test whether orally delivered PT150 could prevent neurological decline in the rotenone model of PD/AD.

Orally delivered PT150 at 30 and 100 mg/Kg/day given *after* exposure to rotenone improved cognitive function in female mice, demonstrating a sex-specific benefit* on cognitive performance



*Although a trend toward improvement was noted in male mice in these initial studies, the data are consistent with the higher prevalence of AD in women than in men.

Additional data available upon request:

- Antiviral
- CNS
- Alcoholism
- Addictions
- Depression

Our Collaborators

Manufacturing led by CapSolutions

PT150 has been produced in the past at a scale of over 200 kilos per batch. Copies of the original process descriptions are available, including methods and impurities.

The compound substance has been produced on a commercial scale and the release methods are validated

CAP SOLUTIONS

The manufacturing of Active Pharmaceutical Ingredients (API's) is a complex process performed on a global basis. Chemical and Pharmaceutical Solutions, Inc., founded in 2002, focuses on the production of API's, their intermediates and the services that are required to produce these products in a highly regulated market place.

James R. Bruno

We have assembled a global network to meet your needs whether your product is in early clinical trials, ready to be launched or a generic product. We work with you to establish the supply lines, solve technical and regulatory problems and prepare you for commercialization.

Our mission is to support the manufacturing process and to maintain the flow of materials through the entire development process. We assure that along the way, your needs are met and that product and quality are on target throughout.

We work closely with Emerging Pharmaceutical Companies to support their clinical trials by assuring the clinical pipeline stays full of product for testing. We also work loosely with Venture Capital groups to review documents and to assist their clients in developing their products. Chemical and Pharmaceutical Solutions also supports strategically, Contract Manufacturing Groups to help them to develop their markets, position their business and look for new technologies!

The PT Management Team

Randi Altschul is an entrepreneur, inventor of new products, author and was an Editorial Advisor/Columnist for the Pharmaceutical Manufacturing and Packing Sourcer International magazine. She is the creator of the world's first disposable cell phone (General Electric), the credit card phone, the programmable debit card, and the paper laptop. She is the only woman to be named a ***"World's Notable Inventor"*** by the World Intellectual Property Organization (WIPO). Ms. Altschul has been CEO of her pharmaceutical company for ten years overseeing a global brain trust of scientists, physicians, clinicians and professionals in the development of therapeutics, diagnostics and devices. She leads the company's' Intellectual Property team in the creation and prosecution of patents. She has led the company's collaborations with the Department of Defense, the Veterans Administration, the National Institutes of Health/ National Institute of Allergy and Infectious Diseases, The National Cancer Institute and numerous Universities and Institutions and the U.S .Department of Agriculture.. Ms. Altschul has been a serial entrepreneur and inventor for more than 35 years, encompassing multiple industries, having licensed more than 250 products around the world.

Neil Theise, MD is a physician/scientist and an international thought leader in clinical medicine (liver disease) and basic science (adult stem cells, human anatomy), publishing in top journals including Cell, Science, Nature, The Lancet. He is a Professor of Pathology at a major New York City medical school. His recent elucidation of a completely novel anatomy of the human Interstitium garnered global attention. He has been a member of the Pop Test & Palisades Therapeutics family of companies from its inception and has been directly involved with development of all its inventions, devices, and pharmacological agents.

John Gregg is a Start-up and pharmaceutical industry veteran. He has extensive experience in forming and successfully exiting biotech companies. His industry expertise of more than 35 years is in worldwide clinical development and commercialization of microbiological products, new anti-infectives, and oncology drugs, most recently with an FDA approval in September 2017 of Solosec (secnidazole). He has spent much of his career directing the commercialization efforts for a large number of antibiotic, anti-protozoal, antifungal and antiviral drugs as well as therapeutics in multiple other therapeutic areas, including immunology and oncology. Mr. Gregg established his reputation in senior marketing and new product planning roles at leading large drug companies including Pfizer, Novartis, Johnson & Johnson, and Bristol-Myers Squibb. In big pharma, Mr. Gregg led global development planning teams for pipeline compounds at all phases of development.

Robert Foerster, MBA
CFO/Business Development

Razvan Ene, PhD
Director,
World Wide Operations

Bob Foerster He is a 28 year Pfizer veteran. He started in the Controllers Division as a Pharmaceutical and R&D Business Analyst, and from there became a Project Manager for operations in Europe, Asia and Africa. His next assignment was as Business Development Director, based in Brussels, for Asia, Africa and Middle East. He then worked as Director Financial Operations Africa and Middle East. Following that, he was promoted to Director/Team Leader New Product Development, responsible for the Neuroscience, Oncology and Metabolic Disease portfolios. He then moved to Tokyo, where he was Sr. Director Business Development Japan, responsible for all development pipeline programs, licensing / partner operations, and strategic planning. Upon returning to New York, he was Sr. Director Commercial Development Emerging Markets. Bob joined the Pop Test & Palisades Therapeutics family of companies in 2015.

Razvan A. Ene, PhD completed management studies at Motorola University where he also lectured on Risk Management. He holds an Applied Physics MSc and a PhD in Electronics and Telecommunications from Turin Polytechnic, Italy. After Motorola he was R&D Director of DDi's Engineering Services Division in the United States. He went on to co-found and be CEO of the innovative Synapto company, dedicated to the development of Smart magnetic sensors. In this last decade, he has been at Elco Group, first as Managing Director of the Engineering Service division and now overseeing all manufacturing operations and research and development on a global level.

WHAT WE WANT FROM YOU

Investment
Collaborations
Out-Licensing
Merger & Acquisitions

Diverse Portfolio of Programs

Our team designs and looks to generate compelling proof of concept data for each program to facilitate global commercialization by a partner/acquirer.

CONTACT:
Randi@PopTestLLC.com
201-943-3770

www.PopTestLLC.com
www.PalisadesTherapeutics.com